EXHIBIT A

Updated 3.10

CURRICULUM VITAE

Name:	Stephen C. Strom, Ph. D.	**Date of Birth:**	July 4, 1952
Home Address:	4382 Maryville Dr. Allison Park, PA 15101	**Birth Place:**	Fort Dodge, Iowa
Phone:	412-370-5430 **(cell)**	**Citizenship**:	U.S.A.
Business Address:	Department of Pathology 200 Lothrop St, 450 BST South University of Pittsburgh Pittsburgh, PA 15261	**E-Mail**	**strom@pitt.edu**
Business Phone: **FAX:**	412-624-7715 412-648-1916		

Education and Training

UNDERGRADUATE:

1970-1974	Westmar College, Le Mars, Iowa	B.A.	Biology and Chemistry

GRADUATE:

1974-1978	University of Kansas Medical Center Dept. of Pharmacology and Toxicology Kansas City, Kansas	Ph.D.	Pharmacology

POST-GRADUATE

1978-1982	Duke University Medical Center Department of Pathology Project: Genetic Toxicology and Carcinogenesis Studying mutation induction, carcinogen metabolism, DNA damage and repair in cultures of rat or human hepatocytes and human fibroblasts.	Dr. George Michalopoulos Postdoctoral Fellowship

Appointments and Positions

1982- 1987	Departments of Radiology and Pharmacology, Duke University Medical Center	Assistant Professor
1988 -1993	Department of Pathology Medical College of Virginia Virginia Commonwealth University	Asst/Associate Professor
7/1/93 -	Department of Pathology University of Pittsburgh	Assoc. Professor/Professor

Consulting Activities

Becton Dickinson and Company, Research Center RTP, NC, 1982
E.P.A., Genetic Toxicology, 1983
E.P.A., Principal Author, Air Quality Criteria for Ozone and Other Photochemical Oxidants, EPA/600/8-84/020dF, August, 1986.
Chapter 9: Chromosomal and Mutational Effects of Ozone.
Rohm & Haas, 1987, Interspecies Comparisons of Xenobiotic Metabolism
Pharmacia and UpJohn, Investigations with Human Hepatocytes, 1998-1999
Stemnion, 2002-2006, Stem Cell Technology
Cambrex-Lonza, 2000 -2009, Human Hepatocyte Isolation and Culture

Special Awards and Recognition

University of Kansas Medical Center: Honors, Comprehensive Oral Examination for Doctorate and Honors, Final Oral Examination
Fellowship from the National Cancer Institute, 1980-1982.
Burroughs Wellcome Fund and Federation for the Societies of Experimental Biology (FASEB) Visiting Professor in Basic Medical Sciences, 2000-2001
Section Editor for Hepatocytes, Cell Transplantation 2000 –
Board of Councilors, Cell Transplantation Society, 2002 –
Board of Councilors, Hepatocyte Users Group, US.
Founding member, Placental Stem Cell Society, 2009 –
President Elect, Cell Transplantation Society, 2009

Investigational New Drug (IND) (1997 – current), approval by the US Food and Drug Administration (FDA) for the isolation and transplantation of human hepatocytes to treat liver disease.
First group in the US group to gain FDA approval to transplant hepatocytes into patients with liver disease.
Strom lab, the first laboratory approved by the FDA for hepatocyte isolation for clinical transplantation.

Publications

1. Uyeki, E. M., Nishimura, T., **Strom**, S. and Bisel, T. U. (1977) Suiciding of Hematopoietic and Tumor Clonal Cells by Tritiated Nucleosides, In Vitro. J. Natl. Cancer Inst. 59: 1031-1033

2. Klaassen, C. D. and **Strom**, S. (1978) Comparison of Biliary Excretory Function and Bile Acid Composition in Male, Female and Lactating Female Rats. Drug Metabolism and Distribution 6: 120-124.

3. **Strom**, S. and Uyeki, E. M. (1979). A Suicide Technique to Study Purine Antimetabolites in Bone Marrow and Tumor Colony Forming Cells. Europ. J. Cancer 15: 415-421.

4. **Strom**, S. Johnson, R. L. and Uyeki, E. M. (1979) Mercury Toxicity to Hematopoietic and Tumor Colony Forming Cells and its Reversal by Selenium In Vitro. Toxicology and Applied Pharmacology 49: 431-436.

5. Kligerman, A. D., **Strom**, S. C. and Michalopoulos, G. (1980) Sister Chromatid Exchange Studies in Human Fibroblast-Rat Hepatocyte Co-Cultures: A New In Vitro System to Study SCEs. Environ. Mutagenesis 2: 157-165.

6. Michalopoulos, G., **Strom**, S. C., Kligerman, A. D., Irons, G. P. and Novicki, D. L. (1981) Mutagenesis Induced by Procarcinogens at the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus of Human Fibroblasts Cocultured with Rat Hepatocytes. Cancer Research 41: 1873-1878.

7. **Strom**, S., Kligerman, A. D., and Michalopoulos, G. (1981) Comparisons of the Effects of Chemical Carcinogens in Mixed Cultures of Rat Hepatocytes and Human Fibroblasts. Carcinogenesis 2: 709-715, 1981.

8. Rosenberg, M. R., **Strom**, S. C. and Michalopoulos, G. (1982) The Effects of Nicotinamide and Hydrocortisone on Gamma-Glutamyl Transferase in Primary Cultures of Rat Hepatocytes. In Vitro 18: 775-782.

9. **Strom**, S. C., Jirtle, R. L., Jones, R. S., Rosenberg, M., Novicki, D. L. Novotny, A., Irons, G., McLain, J. R. and Michalopoulos, G. (1982) Isolation, Culture and Transplantation of Human Hepatocytes. J. National Cancer Institute 68: 771-778.

10. Novicki, D. L., **Strom**, S. C., Jirtle, R. L. and Michalopoulos, G. (1982) Cryopreservation of Isolated Rat Hepatocytes. In Vitro 18: 393-399.

11. Michalopoulos, G., Kligerman, A. D., Cianciulli, H. D., Novotny, A. R., **Strom,** S. C. and Jirtle, R. L. (1982) Liver Regeneration Studies with Hepatocytes in Primary Culture. Cancer Research 42: 4673-4682.

12. **Strom**, S. C. and Michalopoulos, G. (1982) Mutagenesis and DNA Binding of Benzo(a)pyrene in Cultures of Rat Hepatocytes and Human Fibroblasts. Cancer Research 42: 4519-4524.

13. Jirtle, R. L., McLain, J. R., **Strom**, S. C., and Michalopoulos, G. (1982) Repair of Radiation Damage in Noncycling Parenchymal Hepatocytes. British J. of Radiology 55: 847-851.

14. **Strom**, S. C., Jirtle, R. L., and Michalopoulos, G. (1983) Genotoxic Effects of 2-Acetylaminofluorene on Rat and Human Hepatocytes. Environ. Health Persp. 49: 165-170.

15. **Strom**, S. C., Novicki, D. L., Novotny, A. R., Jirtle, R. L., and Michalopoulos, G. (1983). Human Hepatocyte-Mediated Mutagenesis and DNA Repair Activity. Carcinogenesis 4: 683-686.

16. Butterworth, B. E., Earl, L. L., **Strom**, S. C., Jirtle, R. L., and Michalopoulos, G. (1983) Induction of DNA Repair in Human and Rat Hepatocytes by 1,6-Dinitropyrene. Mut. Research 122: 73-80.

17. Butterworth, B. E., Bermudez, E., Smith-Oliver, T., Earle, L., Cattley, R., Martin, J., Popp, J., **Strom**, S. C., Jirtle, R. and Michalopoulos, G. (1984). Lack of Genotoxic Activity of Di(2-Ethylhexyl)Phthalate (DEHP) in Rodent and Human Hepatocytes. Carcinogenesis 5: 1329-1335.

18. Rosenberg, M. R., **Strom**, S. C., Pachman, S., Slotkin, T. A. and Michalopoulos,G. (1986). Induction of Rat Kidney Ornithine Decarboxylase by Nicotinamide Without Concomitant Increase in DNA Synthesis. Carcinogenesis 7: 175-178.

19. Jirtle, R. L., Pierce, L., Crocker, I. R., and **Strom**, S., (1985) Radiation Protection of Rat Parenchymal Hepatocytes with S-2-(3-aminopropylamino) ethyphosphorothioic Acid. Radiotherapy and Oncology 4: 231-237.

20. Marselos, M., **Strom**, S. C., and Michalopoulos, G. (1986) Enhancement of Aldehyde Dehydrogenase Activity in Human and Rat Hepatocyte Cultures by 3-Methyl-Cholanthrene. Cell Biol and Toxicol 2: 257-269.

21. Marselos, M., **Strom**, S. C., and Michalopoulos, G.: (1987) Effect of Phenobarbital and 3-Methylcholanthrene on Aldehyde Dehydrogenase Activity in Cultures of HepG2 Cells and Normal Human Hepatocytes. Chemico-Biological Interactions 62:75-88.

22. Loury, D. L., Smith-Oliver, T. **Strom**, S. C., Jirtle, R. L. Michalopoulos, G. and Butterworth, B. E., (1986) Assessment of Unscheduled and Replicative DNA Synthesis in Hepatocytes Treated in Vivo and in Vitro with Unleaded Gasoline or 2,2,4-Trimethylpentane. Toxicol. Appl. Pharmacol. 85:11-23.

23. Monteith, D., and **Strom**, S. C.: (1987) Metabolism of Benzo(a) pyrene by Human Hepatocytes in Primary Cultures Over a 4-log Dose Range. Carcinogenesis 8:983-988.

24. Eckl, P. M., **Strom**, S. C., Michalopoulos, G., and Jirtle, R. L.: (1987) Induction of Sister Chromatid Exchanges in Cultured Adult Rat Hepatocytes by Directly and Indirectly Acting Mutagens/Carcinogens Carcinogenesis 8: 1077-1083.

25. **Strom**, S. C. (1987) Issues in Biochemical Applications to Risk Assessment: Can In Vitro Studies Assist Us in Species Extrapolation. Environ. Health Persp. 76: 181-184.

26. Alati, T., Van Cleef, M. **Strom**, S. C. and Jirtle, R. L. (1988) Radiation Sensitivity of Adult Human Parenchymal Hepatocytes. Radiation Res. 115: 152-160.

27. Monteith, D., Michalopoulos, G. and **Strom**, S. C. (1988) Metabolism of 2-Acetylaminofluorene in Primary Cultures of Human Hepatocytes: Dose Response Over a Four-log Range. Carcinogenesis 9:1835-1841.

28. Houck, K. A., Michalopoulos, G. M. and **Strom**, S. C. (1989) Introduction of a Ha-ras Oncogene into Rat Liver Epithelial Cells and Parenchymal Hepatocytes Confers Resistance to the Growth Inhibitory Effects of Transforming Growth Factor-Beta. Oncogene 4: 19-25, 1989.

29. Butterworth, B. E., Smith-Oliver, T., Earle, L., Loury, D., White, D., Doolittle, D., Working, P., Cattley, R. C., Jirtle, R. L., Michalopoulos, G. M. and **Strom**, S.C. (1989) Measurement of Chemically-Induced DNA Repair in Primary Cultures of Human Hepatocytes. Cancer Research 49: 1075-1084.

30. Kornstein. M. J., Weber, J., Luck, J., Massey, G. V., **Strom**, S. C., Mc Williams, N. B. (1989) Epstein-Barr Virus-Associated Lymphoproliferative Disorder. Arch. Pathol Lab. Medicine 113: 481-484.

31. Kari, F. W., Driscoll, S. M. Abu-Shakar, A., **Strom**, S. C., Jenkins, W. L., Voloson, J. S., Rudo, K. M., Langenbach, R. L. (1990) Comparative metabolism and genotoxicity of the structurally similar nitrophenylenediamine Dyes, HC Blue 1 and HC Blue 2, in mouse hepatocytes. Cell Biology and Toxicology 6: 139-155.

32. **Strom**, S. C. and Faust, J. B. Activated Oncogenes in Hepatic Neoplasia. Pathobiology 58: 153-167, 1990.

33. Monteith, D. Michalopoulos, G., and **Strom**, S. C. (1990) Conjugation of chemical carcinogens by primary cultures of human hepatocytes. Xenobiotica 20: 753-763.

34. Monteith, D. M., and **Strom**, S. C. A comparison of the inhibition of deacetylase in primary cultures or rat or human hepatocytes effecting metabolism and binding of 2-Acetylaminofluorene. Cell Biol. and Toxicology 6: 269-285, 1990.

35. Monteith, D., Ding, J. H., Chen, Y. T., Michalopoulos, G. and **Strom**, S. C.: Induction of Cytochrome P(1)-450 Specific RNA and Benzo(a)pyrene Metabolism in Isolated Human Hepatocytes. Toxicology and Applied Pharmacology 105: 460-471, 1990

36. Kauma, S. W., **Strom**, S. C. and Turner, T., Interleukin1-β, HLA-DRα and transforming growth factor-β_1 expression in endometrium, placenta, and placenta membranes. Am. J. Obst. Gyn. 163:1430-1437, 1990.

37. Ware, J. L., Maygarden, S. J., Koontz, W. W., Jr., and **Strom**, S. C. (1991) Immunohistochemical detection of c-erbB-2 protein in human benign and neoplastic prostate. Human Pathology 22: 254-258

38. **Strom**, S. C., Faust, J. B. Cappelliti, E., Harris, R. B., and Lalwani, N. D. (1991) Characterization of Liver Epithelial Cells Transfected with myc and/or ras Oncogenes. Digestive Diseases and Sciences. 36: 642-652

39. Lalwani, N. D., Hylemon, P. B., **Strom**, S. (1991) Altered levels of Phosphoinositide metabolites and activation of guanine-nucleotide dependent phospholipase C in rat hepatic tumors. J. Cell Physiol. 147:354-361

40. **Strom**, S.C. (1991) Use of Human Hepatocytes for Investigations of Genetic Toxicology. Proceedings, The Third International Conference: The Use of Human Cells, Tissues and Organs In Research, National Disease Research Interchange Publication, Philadelphia, PA.

41. Maygarden, S. J., **Strom**, S. C. and Ware, J. L. (1991) Localization of epidermal growth factor receptor by immunohistochemical methods in human prostate carcinoma, prostatic intraepithelial neoplasia and benign hyperplasia. Arch. Pathol and Lab. Med. 116: 269-273.

42. Richardson, F. C., **Strom**, S. C., Copple, D. M., Bendele, R. A., Probst, G. S. and Anderson, N.L. (1993) Comparisons of Protein changes in Human and Rodent Hepatocytes Induced by the Rat-Specific Carcinogen Methapyrilene. Electrophoresis 14:157-161.

43. Cappelluti, E. **Strom**, S. C. and Harris, R. B. (1993) Identification of an Elastase-Like Processing Enzyme for Pro-Transforming Growth Factor-alpha. Biochemistry 32:551-560.

44. Schuetz, E. G., Schuetz, J. D., **Strom**, S. C, Thompson. M. T., Molowa, D. T., Fisher, R. A., Molowa, D. T., Li, D., and Guzelian, P. S. (1993) Regulation of human liver cytochromes P450 in Families 3A in Primary and Continuous Culture of Human Hepatocytes. Hepatology 18: 1254-1262.

45. Delaney, B., Koh, K. S., Yang, K. H., **Strom**, S. C. and Kaminski, N. E. (1993) Hepatocyte Growth Factor Possesses Immunoenhancing Activity. Life Sci. 53:89-93.

46. Kocarek, T.A., Schuetz, E.G., **Strom**, S.C., Fisher, R.A., Guzelian, P.S. (1995) Comparative Analysis of Cytochrome P450 3A Induction in Primary Cultures of Rat, Rabbit, and Human Hepatocytes. Drug. Metab. Disp. 23:415-421.

47. Schuetz, E.G., Schuetz, J.D., Thompson, M.T., Fisher, R.A., Madaraga, J.R., and **Strom**, S.C. (1995) Phenotypic Variability in the Induction of P-Glycoprotein mRNA by Aromatic Hydrocarbons in Primary Human Hepatocytes. Mol Carcinogen. 12:61-65.

48. Presnell, S.C., Thompson, M.T., and **Strom**, S.C., (1995) Investigation of the Cooperative Effects of Transforming Growth Factor-alpha and c-myc Overexpression in Rat Liver Epithelial Cells. Mol Carcinogen.12:233-244.

49. Schuetz, J.D., **Strom**, S.C., and Schuetz, E.G., (1995) Induction of P-glycoprotein mRNA by Protein Synthesis Inhibitors is not Controlled by a Transcriptional Repressor Protein in Rat and Human Hepatocytes. J. Cell Physiol. 165:261-271.

50. Kostrubsky, V.E. **Strom**, S.C., Wood, S.G. Wrighton, S.A., Sinclair, P.R.., and Sinclair, J.F. (1995) Ethanol and Isopentanol Increase CYP3A and CYP 2E in Primary Cultures of Human Hepatocytes. Arch Biochem. Biophys. 322:516-520.

51. Schuetz, J.D., Schuetz, E.G., Trotassery, J.V., Guzelian, P.S., **Strom**, S.C., and Sun, D. (1996) Identification of a Novel Dexamethasone Responsive Region in the Human CYP3A5 Gene and its Activation in Human and Rat Liver Cells. Molecular Pharmacol 49: 63-72.

52. Block, G, Locker, J., Bowen, W., Petersen, B, Katyal, S., **Strom**, S., Riley, T., Howard, T. and

Michalopoulos, G.K., (1996) Population Expansion, Clonal Growth, and Specific Differentiation Patterns in Primary Cultures of Hepatocytes Induced by HGF/SF, EGF and TGFα in Chemically Defined (HGM) Medium. J. Cell Biology 132:1133-1149

53. Presnell, S.C., Stolz, D.B., Mars, W.M., Jo, M., Michalopoulos, G.K., and **Strom**, S.C. (1997) Constitutive Expression of TGF-α in Rat Liver Epithelial Cells Results in Modifications of the HGF/C-Met Pathway. Molecular Carcinogenesis. 18: 244-255.

54. **Strom**, S.C., Fisher, R.A. Thompson, M.T., Sanyal, A.J., Cole, P.E., Ham, J.M., and Posner, M.A. (1997) Human Hepatocyte Transplantation in Terminal Liver Failure.Transplantation 63:559-569.

55. **Strom**, S.C., Fisher, R.A., Rubinstein, W.S., Barranger, J.A., Towbin, R.B., Charron, M., R, Mieles, L., Pisarov, L.A., Dorko, K., Thompson, M.T., and Reyes, J. (1997) Transplantation of Human Hepatocytes. Transplantation Proc. 29: 2103-2106.

56. Krill, D., Shuman, M., Thompson, M.T., Becich, M., and **Strom**, S.C., (1997). A Simple Method for the Isolation and Culture of Epithelial and Stromal Cells From Benign and Neoplastic Prostates. Urology. 49:981-988.

57. Fox, I.J. Chowdhury, J.R., Kaufman, S.S., Goertzen, T.C., Chowdhury, N.R., Warkentin, P.I., Dorko, K., Sauter, B.V., and **Strom**, S.C., (1998) Treatment of The Crigler-Najjar Syndrome Type 1 with Hepatocyte Transplantation. New Eng. J. Med. 338:1422-1426.

58. Kostrubsky, V.E., Lewis, L.D., **Strom**, S.C., Wood, G., Schuetz, E.G., Schuetz, J.D., Sinclair, P.R., Wrighton, S.A., and Sinclair, J.F. (1998) Induction of CYP3A by Taxol in Primary Cultures of Human Hepatocytes. Arch Biochem Biophys 355:131-139.

59. Maenpaa, J, Hall, S.D., Ring, B.J., **Strom**, S.C., Wrighton, S.A. (1998) Stimulation In Vitro of CYP3A Mediated Metabolism by a-Naphthoflavone, Terfenedine and Testosterone. Pharmacogenetics 8: 137-155.

60. VanderBranden, M, Wrighton, S.A Elkins, S., Gillespie, J.S., Binkley, S.N., Ring, B.J., Gladberry, M.G., Mullins, D.C., **Strom**, S.C., Jensen, C.B. (1998). Alterations of the catalytic activities of drug-metabolizing enzymes in cultures of human liver slices. Drug Metab. Dispos. 26:1063-1068.

61. Roy-Chowdhury, J.R. **Strom**, S.C., Chowdhury, N.R., Kaufman, S.,(1998) Horslen, S., Fox, I.J., Hepatocyte Transplantation in Humans: Gene Therapy and More. Pediatrics 102: 647-648.

62. Michalopoulos, GK, Bowen, WC, Zajac, VF, Beer-Stolz, D., Runge, D., Watkins, S., Kostrubsky, V., **Strom**, SC.(1999) Morphogenic Events in Mixed Cultures of Rat Hepatocytes and Non-Parenchymal Cells Maintained in Biological Matrices in the Presence of HGF and EGF. Hepatology.29: 90-100.

63. Runge, DM, Runge, D, Dorko, K., Pisarov, LA, Leckel, K., Kostrubsky, VE, Thomas, D, **Strom**, SC, Michalopoulos, GK, (1999) Epidermal Growth Factor and Hepatocyte Growth Factor Receptor activity in Serum-Free Cultures of Human Hepatocytes. J. Hepatol, 30:265-274.

64. **Strom**, SC, Chowdhury, JR, Fox, IJ. (1999) Hepatocyte Transplantation for the Treatment of Clinical Disease. Seminars In Liver Disease. 19:39-48.

65. Nussler, AK, Vergani, G, Gollin, SM, Dorko, K, Gansauge, S, Morris, S, Demetris, AJ, Nomoto, M, Berger, HG, and **Strom** SC. Isolation and Characterization of a Human Hepatic Epithelial-Like Cell Line (AKN-1) From Normal Liver. In Vitro Cell Dev. Biol. 35:190-197, 1999.

66. Su, G.L., Dorko, K., **Strom**, S.C., Nussler, A.K., Wang, S.C. (1999) CD14 Expression and Production by Human Hepatocytes. J. Hepatol. 31:435-442.

67. Kostrubsky, V.E., Ramachandran, V., Venkataramanan, R., Dorko, K., Esplen, J.E., Zang, S., Sinclair, J., Wrighton, S.A., and **Strom**, S.C. (1999) The use of human hepatocytes to study induction of cytochrome P450. Drug Metab. And Disposition 27:887-894.

68. Ramachandran, V., Kostrubsky, V.E., Komoroski, B., Shimin, Z., Dorko, K., Esplen, J.E., **Strom**, S.C., and Venkataramanan, R. (1999) Troglitazone Increases CYP3A Protein and Activity in Primary Cultures of Human Hepatocytes. Drug Metabolism and Disposition 27: 1194-1199.

69. Runge, DM, Runge, D, Foth, H., **Strom**, SC, Michalopoulos, GK. STAT1a/1b. STAT 3 and STAT 5: Expression and Association with c-met and EGF-Receptor in Long-Term Cultures of Human Hepatocytes. Biochem. Biophys. Res. Comm. 265:376-381, 1999.

70. Runge, D. Kostrubsky, V.E., Runge, D.M., Lubecki, K.A., Stolz, D.B., Karathanasis, S.K., Kietzmann, T., **Strom**, S.C., Jungermann, K., and Michalopoulos, G.K. (2000) Serum-Free Long-Term Cultures of Human Hepatocytes: Maintenance of Liver Enriched Transcription Factors and Liver Specific Functions. Biochem. Biophys. Res. Comm. 269: 46-53.

71. Runge, D. Fleig, W.E., Michalopoulos, G.K., **Strom**, S.C., Runge, D.M. (2000) Hepatozytentransplantation. Deutsche Medizinische Wochenschrift. 125: 397-400.

72. Jo, M., Beer-Stolz, D. Esplen, J.E., Dorko, K., Michalopoulos, G.K., **Strom**, S.C. (2000) Cross Talk Between EGFR and c-met Signal Pathways in Transformed Cells. J. Biol. Chem. 275: 8806-8811.

73. Jo, M., Kim, T.Y., Seol, D. Esplen, J.E., Dorko, K., **Strom**, S.C. TNF-Related Apoptosis Inducing Ligand (TRAIL)-Induced Apoptosis in Normal Human Hepatocytes, Nature Medicine (2000) 6: 564-567.

74. Bohnen, N.I., Charron, M., Reyes, J., Rubenstein, W., **Strom**, S.C., Swanson, D. and Towbin. R. (2000) The use of Indium-111 Labeled Hepatocytes to Determine the Biodistribution of Transplanted Hepatocytes through Portal Vein Infusion., J. Nuc. Medicine 25: 447-450.

75. Kostrubsky, V.E., Sinclair, J.F., Ramachandran, V. Venkataramanan, R., Wen, Y.H., Kindt, E., Galchev, V., Rose, K., Sinz, M., **Strom**, S.C. (2000) The Role of Conjugation of Troglitazone in Human and Porcine Hepatocyte Cultures. Drug. Metab. Disposition. 28:1192-1197.

76. Chang, C.C.Y, Sakashita, N., Ornvold, K., Lee, O., Chang, E.T., Dong, R., Lin, S., Lee, C-Y. G. **Strom**, S.C., Kashyap, R., Fung, J.J., Varase, R.F. Jr. Patoiseau J-F, Delhon, A. and Chang, T.Y. (2000) Immunological Quantitation and Localization of ACAT-1 and ACAT-2 in Human Liver and Small Intestine. J. Biol. Chem. 275:28083-28092.

77. Runge, D., Kohler, C., Kostrubsky, V.E., Jagar, D., Lehmann T., Runge, D.M., May, U, Stolz, D.B., **Strom**, S.C., Fleig, W.E. and Michalopoulos, G.K. (2000) Induction of Cytochrome P450 (Cyp)1A1, CYP1A2 and CYP3A4 but Not of CYP1C9, CYP2C19, Multidrug Resistance (MDR-1) and Multidrug Resistance Associated Protein (MRP-1) by Prototypical Inducers in Human Hepatocytes. Biochem.Biophys. Res. Commun. 273: 333-341.

78. Runge, D. Michalopoulos, G.K., **Strom**, S.C. and Runge, D.M. (2000) Recent Advances in Human Hepatocyte Culture Systems. Biochem.Biophys. Res. Commun. 274: 1-3.

79. Fisher, R.A. Bu, D. Thompson, M.T., Tisnado, J., Prasad, U., Sterling, R., Posner, M. and **Strom**, S.C. (2000) Defining Hepatocellular Chimerism in a Liver Failure Patient Bridged with Hepatocyte Infusion. Transplantation 69: 303-307.

80. Venkataramanan, R., Ramachandran, V., Komoroski, B.J., Zang, S., Schiff, P.L., and **Strom**, S.C.. (2000) Milk Thistle, a Herbal Supplement, Decreases the Activity of CYP3A4 and Uridine Diphosphoglucuronosyl Transferase in Human Hepatocyte Cultures. Drug Metab. Dispo. 28:1270-1273.

81. Kuehl, P. Zang, J., Lin, Y., Lamba, J., Assen, M., Schuetz, J., Watkins, P., Daly, A., Wrighton, S., Hall, S, Maurel, P., Relling, M., Brimer, C., Yasuda, K., Venkataramanan, R., **Strom**, S, Thummel, K., Bogsuki, M.S., Schuetz, E. (2001) Sequence Diversity in CYP3A Promoters and Characterization of the Genetic Basis for polymorphic CYP3A5 expression. Nature Genetics 4: 383-391.

82. Lawrence, D., Shahrokh, Z., Masters, S, Achilles, K., Shih, D., Mounho, B., Hillan, K., Totpal, K., DeForge, L., Schow, P., Hooley, J., Sherwood, S., Brush, J., Gooddard, A., Pai., R., Leung, S., Khan, L., Gliniak, B., Bussiere, J., Smith, C., **Strom**, S., Kelly, S., Fox, J., Thomas, D., Ashkenazi, A. (2001) Differential hepatocyte toxicity of recombinantApo2L/TRAIL versions. Nature Medicine 7: 383-385.

83. Zhang, J., Kuehl, P., Green, E.D. Touchman, J.W., Watkins, P., Daly, A., Hall, S., Maurel, P., Relling, M., Briner, C., Yasuda, K., Wrighton, S.A., Hancock, M., Kim, R., **Strom**, S, Thummel, K., Russell, C., Hudson, J.R., Schietz, E.G., Boguski, M.S. The human pregnaneX receptor: genomic structure and identification and functional characterization of natural allelic variants. Pharmacogenetics 11:1-18, 2001.

84. Schuetz EG, **Strom** S, Yasuda K, Lecureur V, Assem M, Brimer C, Lamba J, Kim RB, Ramachandran V, Komoroski BJ, Venkataramanan R, Cai H, Sinal CJ, Gonzalez FJ, Schuetz JD. Disrupted bile acid homeostasis reveals an unexpected interaction among nuclear hormone receptors, transporters, and cytochrome P450. J Biol Chem. (2001) 276:39411-39418.

85. Lamba, J. Lin, Y., Thummel, K., Daly, A. Watkins, P., **Strom**, S., Zang, J., Schuetz, E. (2002) Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. Pharmacogenetics 12:1-12.

86. Radeva, S., Jaruga, B, Hong, F., Kim, W-H, Fan, S, Cai, H, **Strom**, S, Liu, Y, El-Assal, O, Gao, B. Interferon-alpha activates multiple STAT signals and down-regulates c-met in primary human hepatocytes. (2002) Gastroenterology 122:1020-1034.

87. Raucy, J, Mueller, L, Duan, K, Allen, SW, Cai, H, **Strom**, S, Lasker, J. (2002) Expression and

induction of CYP2C P450 enzymes in primary cultures of human hepatocytes. Drug Metab Disp. 302:475-482.

88. Wen, YH, Sahi, J, Urda, E, Kulkarni, S, Zeng, X, Sinclair, JF, Cai, H, **Strom**, SC, Kostrubsky, V. (2002) Effects of bergomottin on drug metabolizing enzymes in primary cultured human and monkey hepatocytes. Drug Metab Disp 30: 977-984.

89. Kocarek, T.A., Dahn, M, Cai, H, **Strom**, SC, Mercer-Haines, N. (2002) Regulation of CYP2B6 and CYP3A expression by hydroxymethylglutaryl coenzyme A inhibitors in primary cultured human hepatocytes. Drug Metab Dispos 30(12):1400-1405.

90. Schuetz, E, Lan, L, Kim, R, Kocarek, T, Schuetz, J, **Strom**, S. (2002) Development of a real-time in vivo transcription assay: Application reveals PXR mediated induction of CYP3A by cancer therapeutic agents. Mol Pharm 62:439-445.

91. Mehdi, H, Manzi, S, Desai, P., Chen, Q., Nestlerode, C, Bontempo, F, Wang, X, **Strom**, SC, Zarnegar, R, Kamboh, M.I. (2003) A Functional polymorphism at the transcriptional initiation site of beta-3 glycoprotein I (apolipoprotein H) associated with reduced gene expression and lower plasma levels of beta 2-glycoportein. Europ J Biochem 270: 230-238.

92. Horslen, SP, McCowan, T.C., Goertzen, T.C., Warkington, P.I., Cai, H., **Strom**, S.C., and Fox, I.J. (2003) Isolated hepatocyte transplantation in an infant with a severe urea cycle disorder. Pediatrics 111: 1262 – 1267.

93. Kostrubsky, V.E., **Strom**, S.C., Hanson, J., Urda, E., Rose, K., Burleigh, J., Zocharski, P., Sinclair, J.F. and Sahi, J. Evaluation of the hepatotoxic potential of drugs by inhibition of bile acid transport in cultured primary human hepatocytes and intact rats. Toxicol Sci 76: 220-228.

94. Wege, H., Chui, M.S., Le, H.T., Cai, H., **Strom**, S.C. and Zern, M.A. (2003) In vitro expansion of human hepatocytes is restricted by telomere-dependent replicative aging. Cell Transplantation 12: 897-906.

95. Cai, H **Strom**, S.C. (2003) Human Hepatocyte Transplantation. Chinese J. General Surgery 12:704-707.

96. Lamba, V., Lamba, J. **Strom**, S. Davila, J., Hancock, M, Yang, W., Frackenthal, J.D., Rosan, P., Ring, B., Wrighton, S. and Schuetz, E.G. (2004) Hepatic CYP2B6 expression: gender and population differences in relationship to CYP2B6 genotype and CAR expression. J. Pharmacol. Exp. Ther. 307: 906-922.

97. Davila, J.C., Thiede, M., **Strom**, S, Miki, T., Cezar, G., and Trosko, J. (2004). Use and application of stem cells in toxicology. Toxicology Sciences. 79: 214-223.

98. Komoroski, B.J., Zang, S., Cai, H. Hutzler, M., Fry, R., Tracy, T., **Strom**, S.C., Venkararamanan, R., (2004) Induction and inhibition by St. John's Wort constituent hyperforin in human hepatocytes. Drug Metab Disp. 32(5):512-518.

99. Assem, M, Schuetz, EG, Leggas, M, Sun, D, Yasuda, K, Reid, G, Zelcer, N, Adachi, M, **Strom**, S,

Evans, RM, Moore, DD, Borst, P, Schuetz, JD. (2004) Interactions between hepatic Mrp4 and Sult2a as revealed by the constitutive androstane receptor and Mrp4 knockout mice. J. Biol. Chem. (2004) 279(21): 22250-22257.

100. Walldorf, J., Aurich H, Cai, H, Runge, D., Christ, B, **Strom** S.C., Fleig, W.E. (2004) Expanding hepatocytes, in vitro, before cell transplantation: donor age dependent proliferative capacity of cultured human hepatocytes. Scand.J. Gastroenterol 39(6): 584-593.

101. Lamba, V., Yasuda, K., Lamba, J., Cline, C., Assem, M., Lin, Y., Davila, J., **Strom**, S and Schuetz, E.G. (2004). PXR/SXR (NR1I2): Splice variants in human tissues including brain and identification of neurosteroids and nicotine as PXR activators. Tox. Applied Pharmacol 199: 251-265.

102. Mu, M, Chen, P., Wu, X, Liu, W, **Strom, S**, Das, S., Cook, E, Rosner, G, Dolan, M.E. (2004) Determination and analysis of single nucleotide polymorphisms and haplotype structure Pharmacogenetics 14:595-605.

103. Tian, H., Ou, J., Aaron, J, **Strom, S**, Venkataramanan, R., (2005) Pharmacokinetics of Tacrolimus and mycophenolic acid are altered, but recover at different times during hepatic regeneration. Drug Metabolism and Dispos. 33:329-335.

104. Tian, H, Ou, **Strom, SC**, Venkataramanan, R, (2005) Activity and expression of various isoforms of uridine diphosphate glucuronyltransferase are differentially regulated during hepatic regeneration in rats. Pharm. Res. 22: 2007-2015.

105. Fang, H-L, **Strom, S.C**, Cai, H., Kocarek, T.A., and Runge-Morris, M. (2005) Regulation of human hepatic hydroxysteroid sulfotransferase expression by the peroxisome proliferators activated receptor alpha transcription factor. Molecular Pharmacology 67:1257-1267.

106. Gross-Steinmeyer, K, Stapleton, P.L., Liu, F., Bammler, T.K., Buhler, D.R., Safe, S.H., **Strom**, S.C., and Eaton, D.L. (2004) Phytochemical-induced changes in gene expression of carcinogen-metabolzing enzymes in cultured human hepatocytes. Xenobiotica, 34:619-632.

107. Ambrosino, G., Varotto, S. **Strom**, S.C., Guariso, G., Franchin, E., Miotto, D., Caenazzo, L., Basso, S., Carraro, P., Valenti, M.L., D'Amico, D., Zancan, L D' Antiga, L.D..(2005) Isolated hepatocyte transplantation for Crigler-Najjar Syndrome, Type 1. Cell Transplantation 14: 151-157.

108. Feng, Y., Zhang, S., Poloyac, S., **Strom**, S.C., Venkataramanan, R. (2005) Determination of 13-O-demethyl tacrolimu in human liver microsomal incubatates using liquid chromatography-mass spectrophotometric assay (LC-MS) J.Chromatog B. Analyt.Technol.Biomed Life Sci. 5: (821) 31-37.

109. Kostrubsky, V. Sinclair, J.F., **Strom**, S.C., Woods, S., Urda, E., Wen, Y.H., Kulkarni, S., Mutlib, A.(2005) Phenobarbital and phenytoin increased acetaminophen hepatotoxicity due to inhibition of UDP-glucuronyltransferases in cultured human hepatocytes. Toxicology Sciences. 87(1) 146-155.

110. Gross-Steinmeyer, K., Stapleton, PL, Tracy, JH, Bammler, TK, Lehmann, T, **Strom, SC**, and Eaton, DL (2005) Influence of matrigel-overlay on constitutive and inducible expression of nine genes encoding drug-metabolizing enzymes in primary human hepatocytes. Xenobiotica 35: 419-438.

111. Komoroski, BJ, Parise, RA, Egorin, MJ, **Strom**, SC, Venkataramanan, R., (2005) Effect of the St. John Wort constituent hyperforin on docetaxel metabolism by human hepatocyte cultures. Clin. Cancer Res. 11:6972-6979.

112. Noreault, T, Kostrubsky, V, Wood, S, Nichols, R, **Strom**, SC, Trask, H., Wrighton, S.A., Jacons, J., Sinclair, P.R., Sinclair, J.F. (2005) Arsenite decreased CYP3A4 and RXR-alpha in cultured human hepatocytes. Drug Metabolism and Disposition. 33(7) 993-1003.

113. Mu, Y., Stephenson, CRJ, Kendall, C, Saini, SPS, Toma, D., Ren, S., Cai, H., **Strom,** S.C., Day, B., Wipf, P., Xie, W. (2005) Synthesis and characterization of a PXR agonist with unique species – dependent sterioselectivity. Molecular Pharmacology (In Press).

114. Hussain, S **Strom**, S.C., Kirby, M.R., Z, Burns, S, Langemeijer, S., Ueda, T., Hsieh, M. Tisdale, JF. (2005) Sidepopulation cells derived from adult human liver generate hepatocyte-like cells in vitro. Digestive Diseases and Sciences 50: 1755-1763.

115. Miki, T. Lehmann, T, Cai, H, Stolz, D.B., **Strom**, S.C. (2005) Stem cell characteristics of amniotic epithelial cells. Stem Cells 23: 1549-1559.

116. Monga, Satdarshan P.S.Hout, M., Baun, M., Micsenyi, Y, Muller, P, Tummalapalli, L., Ranade, A, Luo, J-H., **Strom, S.C**., Gerlach, J.C. (2005) Mouse fetal liver cells in artificial capillary beds in three-dimensional four-compartment bioreactors. Am. Journal Pathol. 167: 1279-1292.

117. Venkataramanan, R. Komoroski, B. **Strom**, S.C. (2006) In vitro and in vivo assessment of herb drug interactions. Life Sciences 78: 2105 – 2115.

118. Ramirez, J., Komoroski, B.J., Mirkov, S, Graber, AY, Frankenthal, DL, Schuetz, EG, Das, S, Ratain, MJ, Innocenti, F., **Strom, SC**. (2006) Study of the genetic determinants of UGT1A1 inducibility by Phenobarbital in cultured human hepatocytes. Pharmacogenet. Genomics 16: 79-86.

119. Lamba, J, **Strom S**, Venkataramanan, V, Thummel, KE, Lin, YS, Liu, W, Cheng, C, Lamba, V, Watkins, PB, Schuetz, EG. (2006) MDR1 genotype is associated with hepatic cytochrome P450 3A4 basal and induction phenotype. Clin. Pharmacol. Ther 79: 325-338.

120. Lamba, JK, Chen, X, Lan, LB, Kim, JW, Wei Wang, X, Relling, MV, Kazuto, Y, Watkins, PB, **Strom,** SC, Sun, D, Schuetz, JD, Schuetz, EG. (2006) Increased CYP3A4 copy number in TONG/HCC cells but not in DNA from other humans. Pharmacogenet. Genomics 16: 415-427.

121. Kostrubsky, V., **Strom, S.C**., Kalgutkar, A., Kulkarni, S., Atherton, J., Mireles, R., Kubik, R., Hanson, J., Urda, E., Mutlib, A. (2006). Inhibition of hepatobiliary transporters as a predictive method for clinical hepatotoxicity of nefazodone. Tox. Sci. 90(2) 451-459.

122. Nussler, A., Konig, S., Ott, M., Sokal, E., Christ, B., Thasler, W., Bulport, M, Gabelein, G., Schormann, W., Schulze, M., Ellis, E., Kraemer, M., Nocken, F, Fleig, W., Manns, M., **Strom, S.C.,** Hengstler, J.G. (2006) Present status and perspectives of cell based therapies for liver diseases. J. Hepatol. 45: 144-159.

123. Hariparsad, N, Sane, R, **Strom**, SC, Desai, PB. (2006) In vitro methods in human drug biotransformation research: implications for cancer chemotherapy. Toxicol. *In Vitro.* 135-153.

124. Chen, K., Li, F., Li, J., Cai, H., **Strom, S.**, Bisello, A., Kelley, D.E., Friedman-Einat, M., Skibinski, G., McCrory, M.A., Szalai, A., Zhao, A.Z. (2006) Induction of leptin resistance through direct interaction of c-reactive protein with leptin. Nature Med. 12: 425-432.

125. **Strom** S. Bruzzoni, P. Cai, H., Ellis, E. Lehmann, T. Mitamura, K, Miki, T. (2006) Human hepatocyte transplantation, clinical experience. Cell Transplantation 15 (Suppl) S105-S110.

126. Finkelstein, D, Lamba, V, Assem, M, Rengelshausen, J, Yasuda, K, **Strom**, S, Schuetz, EG. (2006) The ADME transcriptome in hispanic versus while donor livers: evidence of a globally enhanced NR113 (CAR, Constitutive androstane receptor) gene signature. Xenobiotica 36989-1012.

127. Li, T, Kong, X, Owsley, E., Ellis, E. **Strom, S.**, Chaing, J.Y. (2006).Insulin regulation of cholesterol 7alpha-hydroxylase expression in human hepatocytes: roles of forkhead box O1 and sterol regulatory element-binding protein 1c. *J Biol Chem* 281, 28745-54.

128. Luo, J, Ren, B, Keryanov, S, Tseng, GC, Rao, UN, Monga, SP, **Strom, S.**, Demetris, A. J., Nalesnik, M., Yu, YP, Ranganathan, S., Michalopoulos, G. K. (2006). Transcriptomic and genomic analysis of human hepatocellular carcinomas and hepatoblastomas. *Hepatology* 44, 1012-24.

129. Yamamoto, N., Wu, J., Zhang, Y., Catana, A. M., Cai, H., **Strom, S.**, Novikoff, P. M., and Zern, M. A. (2006). An optimal culture condition maintains human hepatocyte phenotype after long-term culture. *Hepatol Res* **35,** 169-77.

130. Mirkov, S., Komoroski, B. J., Ramirez, J., Yoder Graber, A., Ratain, M. J., **Strom, S. C.**, and Innocenti, F. (2007). Effects of green tea compounds on irinotecan metabolism. *Drug Metab Dispos.* 35: 228-233.

131. Page, J. Johnson, M, Olsavsky, K **Strom, S**, Zarbl, H, Omiecinski, C. Gene expression profiling of extracellular matrix as an effector of human hepatocyte phenotype in primary culture. (2007) Toxicol Sci.. 97: 384-397.

132. Olsavsky, K.M., Page, J.L., Johnson, M.C., Zarbl, H., **Strom, S.C.**, and Omiecinski, C. (2007) Gene expression profiling and differentiation assessment in primary human hepatocyte cultures, established hepatoma cell lines, and human liver tissues. Toxicol Appl Pharmacol. 222:43-56.

133. Stoner, MA, Auerbach, SS, Zamule, SM, **Strom, SC**, Omiecinski, CJ. (2007) Transactivation of a DR-1 PPRE by human constitutive androstane receptor variant expressed from internal protein translation start sites. Nucleic Acids Res. 2177-2190.

134. He, N., Cai, H. B., Xie, H. G., Collins, X., Edeki, T. I., and **Strom, S. C**. Induction of cyp3a in primary cultures of human hepatocytes by ginkgolides a and B. Clin Exp Pharmacol Physiol, *34:* 632-635, 2007.

135. Miki, T., Mitamura, K., Ross, M. Stolz, D.B., **Strom, S.C.**, (2007) Identification of stem cell marker positive cells in human placenta.. Rep. Immunol. 75:91-96.

136. Chandler, R.J., Tsai, M.S., Dorko, K. Sloan, J., Korson, M., Freeman, R., **Strom, S.C.**, Vendetti, C.P. (2007) Adenoviral-mediated correction of methylmalonyl-CoA murtase deficiency in *mut*^{0} human hepatocytes. BMC Med Genet (2007) 8:24-30.

137. Azuma, H., Paulk, N., Ranade, A., Dorrell, C., Al-Dhalamy, M., Ellis, E., **Strom, S.C.,** Kay, M.A., Finegold, M., Grompe, M. (2007) A robust system for the *in vivo* expansion of human hepatocytes. Nature Biotech. (2007) 25: 903-910.

138. Kostrubsky, S.E.,**Strom, S.C.,** Ellis, E., Nelson, S.D. Mutlib, A.E. (2007) Hepatoxicity and metabolism of flutamide. Drug-drug interaction with acetaminophen involving phase I and II metabolites. Chem Res Toxicol (2007) 1503 -1512.

139. Duniec-Dmuchowski, Z. Ellis, E., Strom, S.C. Kocarek, T.A. (2007) Regulation of CYP3A4 and CYP2B6 expression by liver x receptor agonists. Biochem. Pharmacol. 74: 1535-1540.

140. Fang, H. L., **Strom, S. C.**, Ellis, E., Duanmu, Z., Fu, J., Duniec-Dmuchowski, Z., Falany, C. N., Falany, J. L., Kocarek, T. A., and Runge-Morris, M. (2007) Positive and Negative Regulation of Human Hepatic Hydroxysteroid Sulfotransferase (SULT2A1) Gene Transcription by Rifampicin: Roles of Hepatocyte Nuclear Factor 4{alpha} and Pregnane X Receptor. J Pharmacol Exp Ther, 323:586-598.

141. Kotokorpi, P., Ellis, E., Parini, P., Nilsson, L. M., **Strom, S.**, Steffensen, K., Gustafsson, J. A., and Mode, A. (2007) Physiological differences between human and rat primary hepatocytes in response to LXR activation by GW3965. Mol Pharmacol. 72: 947-955.

142. Zou, C., Ma, J., Wang, X., Guo, L., Zhu, Z., Stoops, J., Eaker, A. E., Johnson, C. J., **Strom, S.,** Michalopoulos, G. K., Defrances, M. C., and Zarnegar, R. (2007) Lack of Fas antagonism by Met in human fatty liver disease. Nat Med 13: 1078-1985.

143. Nilsson, LM, Sjovall, J, **Strom, SC**, Bodin, K, Nowak, G., Einarsson, C. Ellis, E. Ethanol stimulates bile acid formation in primary human hepatocytes. Biochem Biophys Res Commm. 364: 743-747.

144. Parolini, O., Alviano, F., Bagnara, G. P., Bilic, G., Buuhring, H. J., Evangelista, M., Hennerbichler, S., Liu, B., Magatti, M., Mao, N., Miki, T., Marongiu, F., Nakajima, H., Nikaido, T., Portmann-Lanz, C. B., Sankar, V., Soncini, M., Stadler, G., Surbek, D., Takahashi, T. A., Redl, H., Sakuragawa, N., Wolbank, S., Zeisberger, S., Zisch, A., and **Strom, S. C.** Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells. Stem Cells, *26:* 300-311.

145. Miki, T, Marongiu, F., Ellis, E. and **Strom, S.** Isolation of Amniotic Epithelial Stem Cells. Appendix 8.2. Current Protocols in Stem Cell Biology **1E.3,** 1E.3.1-1E.3.9.

146. Song, K-H, **Strom, S.C.**, Ellis, E., Chiang, J.Y.L. (2007) Hepatocyte growth factor signaling pathway induces c-Jun and SHP to inhibit cholesterol 7α-hydroxylase and bile acid synthesis in human hepatocytes. Hepatology 46: 1993-2002.

147. Page, JL, **Strom, SC**, Omiecinski, CJ, (2007) Regulation of the human cathepsin E gene by constitutive androstane receptor. Arch Biochem Biophys 467: 132-138.

148. Lamba, J., Lamba, V., **Strom, S.**, Venkataramanan, R., and Schuetz, E. (2008) Novel single nucleotide polymorphisms in the promoter and intron 1 of human pregnane X receptor/NR1I2 and their association with CYP3A4 expression. Drug Metab Dispos, *36:* 169-181.

149. Wada, T., Kang, H. S., Angers, M., Gong, H., Bhatia, S., Khadem, S., Ren, S., Ellis, E., **Strom, S.** C., Jetten, A. M., and Xie, W. (2008) Identification of oxysterol 7alpha-hydroxylase (Cyp7b1) as a novel retinoid-related orphan receptor alpha (RORalpha) (NR1F1) target gene and a functional cross-talk between RORalpha and liver X receptor (NR1H3). Mol Pharmacol, *73:* 891-899.

150. Zamule, S. M., **Strom, S. C.,** and Omiecinski, C. J. (2008) Preservation of hepatic phenotype in lentiviral-transduced primary human hepatocytes. Chem Biol Interact, *173:* 179-186.

151. Yasuda, K., Ranade, A., Venkataramanan, R., **Strom, S.**, Chupka, J., Ekins, S., Schuetz, E., and Bachmann, K. (2008) A comprehensive in vitro and in silico analysis of antibiotics that activate pregnane X receptor and induce CYP3A4 in liver and intestine. Drug Metab Dispos, *36:*1689-1697.

152. Schadt, E. E., Molony, C., Chudin, E., Hao, K., Yang, X., Lum, P. Y., Kasarskis, A., Zhang, B., Wang, S., Suver, C., Zhu, J., Millstein, J., Sieberts, S., Lamb, J., GuhaThakurta, D., Derry, J., Storey, J. D., Avila-Campillo, I., Kruger, M. J., Johnson, J. M., Rohl, C. A., van Nas, A., Mehrabian, M., Drake, T. A., Lusis, A. J., Smith, R. C., Guengerich, F. P., **Strom, S. C.**, Schuetz, E., Rushmore, T. H., and Ulrich, R. (2008) Mapping the genetic architecture of gene expression in human liver. PLoS Biol, *6:* e107.

153. Goyak, K. M., Johnson, M. C., **Strom, S. C.**, and Omiecinski, C. J. (2008) Expression profiling of interindividual variability following xenobiotic exposures in primary human hepatocyte cultures. Toxicol Appl Pharmacol, *231:* 216-224.

154. Sharma, S., Ou, J., **Strom, S.**, Mattison, D., Caritis, S., and Venkataramanan, R. (2008) Identification of enzymes involved in the metabolism of 17alpha-hydroxyprogesterone caproate: an effective agent for prevention of preterm birth. Drug Metab Dispos, *36:* 1896-1902.

155. Basma, H, Soto-Gutierrez, A, Yannam, GR, Liu, L, Ito, R, Yamamoto, T, Ellis, E, Carson, SD, Sato, S, Chen, Y, Muirhead, D., Navarro-Alverez, N, Wong, RJ, Roy-Chowdhury, J, Platt, J, Mercer, DF, Miller, JD, **Strom, SC**, Kobayashi, N, Fox, I. (2009) Differentiation and transplantation of human embryonic stem cell-derived hepatocytes. Gastroenterology 136:990-999.

156. Miao, J, Xiao, Z, Kanamaluru, D, Min, G, Yau, PM, Veenstra, TD, Ellis, E, **Strom, S**, Suino-Powell, K, Xu, HE, Kemper, JK, Bile acid signaling pathways increase stability of smallheterodimer partner (shp) by inhibiting ubiquitin-proteasomal degradation. Genes and Development 23:986-996.

157. Li, T, Ma, H, Park,YJ, Lee, YK, **Strom,SC**, Chiang, JY. (2009) Forkhead box transcription factor O1 inhibits cholesterol 7-alpha hydroxylase in human hepatocytes and in high fat diet-fed mice. BBA- Molec Cell Biol of Lipids. 1791: 991-996.

158. Song, KH, Li, T, Owsley, E, Strom, S, Chiang, JY. (2009) Bile acids activate fibroblast growth factor 19 signaling in human hepatocytes to inhibit cholesterol 7-alpha hydroxylase gene expression. Hepatology 49: 297 – 305.

159. Skvorak, KJ, Paul, HS, Dorko, K. Marongiu, F, Ellis, E Chace, D., Ferguson, C, Gibson, KM, Homanics, GE and **Strom SC.** (2009) Hepatocyte Transplantation Improves Phenotype and Extends Survival in a Murine Model of Intermediate Maple Syrup Urine Disease. Molecular Therapy 17:1266-1273.

160. Fujimoto, KL, Miki, T, Liu, LJ, Hashizume, R., Strom, SC, Wagner, WR, Keller, BB, Tobita, K. (2009) Naïve rat amnion-derived cell transplantation improved left ventricular function and reduced myocardial scar of post-infarcted heart. Cell Transplantation 18: 477-486.

161. Sharma, S. Venkataramanan, R, Caritis, S, Dorko, K, **Strom, SC**. (2009) Metabolism of 17α-hydroxyprogesterone caproate by fetal liver: A new agent for preventing pre-term labor. Drug Metabolism and Disposition (In Press) .

162. Skvorak, K,J, Hager, E.J., Arning, E, Bottinglieri, T., Paul, HS, **Strom, SC**, Homanics, GE, Sun, Q, Jansen, EW, Jakobs, C, Zinnanti, WJ, Gibson, K.M. (2009) Hepatocyte transplantation corrects selected neurometabolic abnormalities in murine intermediate Maple Syrup Urine Disease (iMSUD). In BBA Mol Basis of Disease. 1792: 1004-1010.

163. Moody, DE, Fang, WB, Lin, SN, Weyant, DM, **Strom, SC**, Omiecinski, CJ. (2009) The effect of rifampicin and nelfinavir on the metabolism of methadone and buprenormorphine in primary cultures of human hepatocytes. Drug Metabolism and Disposition 37:2323-2329.

164. Gross-Steinmeyer, K, Stapleton, PL, Tracy, JH, Bammler, TK, **Strom, SC**, Buhler, D, Eaton, DL. (2009) Modulation of aflatoxin B1-mediated genotoxicity in primary cultures of human hepatocytes by diindolymethane, curcumin and xanthohumols. Tox, Sci , 112:303-310.

165. Ullrich, A, Stolz, DB, Ellis, EC, **Strom, SC**, Michalopoulos, GK, Hengstler, JG, Runge, D. (2010) Long-term cultures of primary human hepatocytes as an alternative to drug testing in animals. Altex 26:295-302.

166. Schroeder, JC, Dinatale, BC, Murray, IA, Flaveny, CA, Liu, Q, Laurenzana, EM, Lin, JM, **Strom, SC**, Omiecinski, CJ, Amin, S, Perdew, GH. (2010) The uremic toxin 3-indoxyl sulfate is a potent endogenous agonist for the human aryl hydrocarbon receptor. Biochemistry 49: 393-400.

167. Parolini, O, Alviano, F, Bergwerf, I, DeBari, C, DeWaele, P, Dominici, M, Evangelista, M, Falk, W, Hennerbichler, S, Hess, D, Lanzoni, G, Liu, B, Marongiu, F, McGuckin, C, Mohr, S, Nolli, M, Ofir, R, Ponsaertz, P, Romagnoli, L, Solomon, A, Soncini, M, **Strom, S**, Surbek, D, Venkatachalam, S, Wolbank, S, Zeisberger, S, Zeitlin, A, Zisch, A, Borlongan, C. (2010) Towards cell therapy uusing placenta-derived cells: disease mechanisms, cell biology, preclinical studies and regulatory aspects at the round table. Stem Cell and Development 19: 143-154.

168. Lamba, V, Panetta, JC, **Strom, S**, Schuetz, EG. (2010) Genetic predictors of interindividual variability in hepatic CYP3A4 expression. J Pharmacol. Exp. Therapeutics 332: 1088 – 1099.

169. Chen, F, Ellis, E, **Strom, SC**, Shneider, BL (2010) ATPase Class 11 Type 8B member 1 protein kinase C Zeta induces the expression of the cannicular bile salt export pump in human hepatocytes. Pediatric Research 67: 183-187.

170. Chudhry, AS, Urban, T, Lamba, J, Birnbaum, A, Remmel, R, Subramanian, M, **Strom, S**, You, J, Kasperaviciute, D, Catarino, CB, Radtke, R, Sisidiya, S, Goldstein, D, Schuetz, EG. (2010) CYP2C9*1B promoter polymorphisms, in linkage with CYP2C19*2, affect phenytoin autoinduction of clearance and maintenance dose. J. Pharmacol Exp Therapeutics. 332: 599-611.

171. Miki, T, Marongiu, F, Dorko, K, Ellis, E, **Strom, SC** (2010) Isolation of amniotic epithelial stem cells. Current Protocols in Stem Cell Biology Unit 1E3.

172. Marongiu, F., Gramignoli, R, Sun, Q, Tahan, V, Miki, T, Dorko, K, Ellis, E and **Strom, S.** (2010) Isolation of Amniotic Mesenchymal Stem Cells. Current Protocols in Stem Cell Biology. Chapter 1, Unit 1E5.

173. Sellaro, TL, Ranade, A, Falk, D, McCabe, G, Dorko, K, Badylak, SF, **Strom, SC**. (2010) Maintenance of human hepatocytes function, *in vitro*, by liver-derived extracellular matrix gels. Tissue Engineering Part A 16: 1075-1082.

174. Sharma, S. Venkataramanan, R, Caritis, S, **Strom, SC**. (2009) Metabolism of 17α-hydroxy-progesterone caproate in Mice, Rats, Dogs, Pigs, Rabbits and Baboons: A comparison with human liver microsomes and fresh human hepatocytes. Drug Metabolism and Disposition (In Revision).

175. Sharma, S, Ellis, E.C, Venkataramanan, R, Cretis, S, Dorko, K, **Strom, SC**. Expression and activity of transporters in fetal and human hepatocytes: A comparison with adult human hepatocytes. (In revision).

176. Shufeng Liu, Wayne Kuo, Wei Yang, Gregory A. Gibson, Kenneth Dorko, Simon C. Watkins, Stephen C. Strom, Tianyi Wang. Human Occludin extracellular loop 2 is critical for dynamin-dependent HCV entry. Journal of Biological Chemistry (In revision)

Invited Editorials, Commentary or Reviews

1. Schuetz, E., and **Strom**, S.C. (2001) Promiscuous regulator of xenobiotic removal. Nature Medicine 7:536-537, 20.

2. **Strom**, SC, Fisher, RA, (2003) Hepatocyte Transplantation: New possibilities for therapy. Gastroenterology 124: 568-571, 2003.

3. **Strom** S.C. Bigger may not be better when it comes to hepatocytes. (2006) Liver Transplantation 12:16-18.

4. Bruzzone, P and **Strom,** SC. (2006) Historical aspects of hepatocyte transplantation. Transplant Proc. 38: 1179-1180.

5. Fisher, RA, and Strom, SC. (2006) Human hepatocyte transplantation: worldwide results. Transplantation 82: 441-449.

6. Miki, T. Strom, SC, Placental-derived multipotent stem cells (2006) Stem Cell Reviews 2: 133-142.

7. Fox, I. J. and Strom, S. C. To be or not to be: generation of hepatocytes from cells outside the liver. Gastroenterology, *134:* 878-881, 2008.

Chapters in Books

1. Michalopoulos, G., Biles, C., **Strom**, S.C., and Russel, F. (1979) Studies in Hepatocarcinogenesis Using Primary Cultures of Hepatocytes. In: The Liver: Quantitative Aspects of Structure and Function, R. Preissig and J. Bircher, Editors, Editio Cantor.

2. **Strom**, S.C. and Michalopoulos, G. (1982) Collagen as a Substrate for Cell Growth and Differentiation. Methods in Enzymology, Volume on Structural and Contractile Proteins, L. Cunningham, Editor, 82: 544-555.

3. Butterworth, B.E., Doolittle, D.J., Working, P.K., **Strom**, S.C., Jirtle, R.L. and Michalopoulos, G. (1983). Chemically-Induced DNA Repair in Rodent and Human Cells. In: Banbury Report 13: 101-122.

4. Michalopoulos, G., **Strom**, S.C., Novotny, A.R., Novicki, D.L. and Jirtle, R.L. Human Hepatocytes in Primary Culture: Applications in Studies of Human Carcinogenesis. In: In Vitro Models for Cancer Research Vol. II M. Webber, ed. CRC Press, pp 9-21.

5. Michalopoulos, G., **Strom**, S.C. and Jirtle, R.L., (1986) Use of Hepatocytes for Studies of Mutagenesis and Carcinogenesis. In, Isolated and Cultured Hepatocytes, A. Guillouzo and C. Gugen-Guillouzo, ed., John Libbey Eurotext, London. pp 333-352.

6. **Strom**, S.C., Monteith, D.L., Manoharan, K. and Novotny, A.L. (1987) Genetic Toxicology Studies with Human Hepatocytes. In, The Isolated Hepatocyte: Use In Toxicology and

Xenobiotic Transformation,E.J. Rachman and G. Padilla, ed. Academic Press, Inc. Orlando Florida, pp 265-280.

7. Isom, H.C., and **Strom**, S.C. Role of Viral and Cellular Oncogenes and Growth Factors in Hepatocarcinogenesis in Culture and In Vivo. In: The Role of Cell Types in Hepatocarcinogenesis. A.E. Sirica, ed. 1992, CRC Press, Inc. pp 265-298.

8. **Strom**, S.C., Pisarov, L.A., Dorko, K.D., Thompson, M.T. Schuetz, E.G., Schuetz, J.D. (1996) The Use of Human Hepatocytes to Investigate the Regulation of Cytochrome P450 Genes, Methods in Enzymology 272: 388-401.

9. **Strom**, S.C., Fisher, R.A., Pisarov, L.A., Dorko, K., Thompson, M.T. and Reyes, J. (1998) Human Hepatocyte Transplantation., In:. Hepatocyte Transplantation, M.Mito and M. Sawa, Editors, Karger Landis Publishing Co., Austin TX, 325-341.

10. **Strom**, S.C., Dorko, K., Thompson, M.T., Pisarov, L.A., Nussler, A.K. (1998) Large Scale Isolation and Culture of Human Hepatocytes.In Ilots de Langerhans et hepatocytes. Vers une ulilization therapeutique. Le Editions INSERM, Paris pp 195-205.

11. O'Connell, J.F., Cox, S., Buontempo, P., Skelton, A., Pisarov, L.A., Dorko, K. and **Strom**, S.C. (1998) Primary Human Hepatocyte Cultures for the Study of Hepatitis C Virus (HCV). Methods in Molecular Medicine:Hepatitis C Protocols. 1998 Humana Press, Totowa, NJ. pp 495-500.

12. Fisher, R.A. and **Strom**, S.C. Human Hepatocyte Transplantation: Biology and Therapy In Press, Cultured Hepatocytes In Hepatocyte: Biology and Application, M. Berry and A. Edwards ED., Kluwer Academic Publishers, London, 1999.

13. Nakazawa, F, Cai, H, Dorko, K, Abdelmeguid, A, Miki, T, Walldorf, J, Lehmann, T, **Strom**, SC. Human hepatocyte isolation from cadaver donors. Proceedings of Falk Symposium –126 Hepatocyte Transplantation, Kluwer Academic Publishers, Lancaster, UK , 2002.

14. Mitamura, K. Ellis, E., Miki, T. **Strom, S.C**. (2007) Hepatocyte transplantation for liver disease. In New Frontiers in regenerative medicine, Springer Science and Business media, Japan, Pages 3-7.

15. **Strom** S. Ellis, E. (2008) Human hepatocyte transplantation, clinical experience. *Principles of Regenerative Medicine*, edited by Anthony Atala, Robert Lanza, James A. Thomson, and Robert M. Nerem. Academic Press/Elsever 30 Corporate Drive, Suite 400 Burlington, MA 01803 (USA) ISBN 978-0-12-369410-2

16. Davila, JC, Xu, JJ, Hoffmaster, KA, Obrien, PJ, **Strom, SC.** (2007) Current *in vitro* models to study drug-induced liver injury. In Hepatotoxicity: From genomics to *in vitro* and *in vivo* models. Edited by SC Sahu, 2007 John Wiley and Sons, Ltd.

17. Miki, T, Marongiu, F, Ellis, EC, Dorko, K, Mitamura, K, Ranade, A, Gramignoli, R, Davila, J, **Strom, SC**. (2009) Production of hepatocyte-like cells from human amnion. Anil Dhawan, Robin D. Hughes (eds) Humana Press, In, Hepatocyte Transplantation 481:155-168.

18. Marongiu, F, Gramignoli, R, Miki, T., Ranade, A, Ellis, WCS, Dorko, K, Davila, J, **Strom, SC**.

Amniotic epithelial cells in regenerative medicine. Perinatal Stem Cells, Chapter 10 pp 159-167.

19. Dhawan, A, **Strom, S**, Sokal, E, Fox, I. (2009) Hepatocyte transplantation. In, Hepatocytes, Patrick Maurel (ed) 2009, Humana Press/Springer Science+Business Media, LLC, 233 Spring Street, NewYork, NY, 10013 (USA) Chapter 29, pp, 525-534. ISBN 978-1-60761-687-0, DOI 10.1007/978-1-60761-687-0

20. **Strom, S**, Davila, J, Grompe, M. (2009) Chimeric mice with humanized liver: tools for the study of drug metabolism, excretion and toxicity. In, Hepatocytes, Patrick Maurel (ed), Humana Press/Springer Science+Business Media, LLC, 233 Spring Street, NewYork, NY, 10013 (USA) Chapter 27, pp, 491-510. ISBN 978-1-60761-687-0, DOI 10.1007/978-1-60761-687-0

21. **Strom** S. Ellis, E. (In Press) Cell Therapy for liver disease: From hepatocytes to stem cells. *Principles of Regenerative Medicine*, edited by Anthony Atala, Robert Lanza, James A. Thomson, and Robert M. Nerem. Academic Press/Elsever 30 Corporate Drive, Suite 400 Burlington, MA 01803 (USA)

22.

PROFESSIONAL ACTIVITIES

TEACHING

Duke University (1982-1987)

Mammalian Toxicology (PHR 354) Director, Dr. M. Abou Donia
3 Hours covering principles of chemical carcinogenesis and the causes of human cancer

Principles of Pharmacology and Toxicology (PHR 334), Dr. Gerald Rosen, Director, 9 hours covering basic cell biology/cancer biology, chemical carcinogenesis, mutagenesis, oncogenes and cancer induction.

General Pathology for Toxicologists (PTH 382), Dr. Doyle Graham Director, 2 hours covering basic principles and activation of oncogenes and the molecular aspects of cell growth and cancer.

Cancer Biology, Dr. George Michalopoulos, Director, 4 hours, role of oncogenes in normal and neoplastic cell growth.

Radiation Biology for Radiology Residents, Dr. Randy Jirtle, Director, 3 hours covering the genotoxic effects of radiation on developing systems, DNA damage and repair and radiation carcinogenesis.

Member , Graduate Faculty in Pharmacology and Toxicology
Primary faculty advisor, graduate students, Zahra Salehi, M.S. John Faust, Ph.D., 1990
Member, of oral exam and thesis advisory committee for 10 additional graduate students.

Medical College of Virginia/Virginia Commonwealth University (1988-1993)

Pathology 570, Experimental Approaches to Tumor Biology (Dr. Joy Ware, Director)

three hrs of lecture and discussion on general principles of carcinogenesis, mutagenesis and cancer induction and basic mechanisms of signal transduction in normal and transformed cells.

Pharmacology PMC 638 Advanced Toxicology (Dr. Norbert Kaminski, Director) two hrs, covering molecular mechanisms of carcinogenesis.

Pharmacology PMC 625 Biochemical Pharmacology (Dr. Larry Povirk, Director), three hrs covering molecular mechanisms of oncogene activation and their cellular consequences.

Surgical Pathology Lectures to Residents
Modern Techniques in Molecular Biology. Coveringand explaning molecular biological techniques the residents will encounter in daily reading of scientific literature, their uses and limitations.

Radiation Oncology Residents, Principals of Radiobiology, two lectures covering all aspects of Oncogenes, Growth Factors and Cellular Transformation.

Faculty advisor, graduate student, Sharon Presnell
Member, thesis committee for seven graduate students.
Faculty advisor for two medical students in the summer research in Pathology program, 1988-1989. Maria Poggi, won first place in the departmental competition in 1989.
Dean's Representative, Oral Examination May, 1990
Member: Pathology Graduate Program Committee (1989-1993)
Member: MCV, Four Year Subject Matter Committee (1989-1993)
Reviewer/Judge of Research Papers for Forbes Day (1988-1992)
Reviewer Research Proposals (In House, (1989-1993) for A.D. Williams, American Cancer Society
Director, MCV/Massey Cancer Center, Human Tissue Acquisition Facility, (1990-1993)
Program Director, Massey Cancer Center , Program in Carcinogenesis and Tumor Biology 1990 -1993.

University of Pittsburgh (July 1993-present)

Pathobiology, MSCMP2740 The pathiobiology and molecular basis of human diseases. Roy Frye and Cristian Achim, directors. Three lectures (3 hrs) covering liver, alcoholic injury, necrosis, fibrosis, regeneration, carcinogenesis and viral hepatitis. (1998 -2001)
Cancer Biology and Therapeutics, MSCMP 3710 and MSPHL 3310
S. Katyal and J. Yalowich, directors. 2 lectures (2 hrs) covering chemical carcinogenesis, DNA damage, nutrition and cancer.(1996 – 2009).
Cell Structure, Metabolism and Nutrition. Medical Course 5111, S. Morris, director
PBL Facilitator, 6 cases, 42 contact hours. (1998 – 2004), 1 session 4 contact hrs 2006.
MSCMP 2730: Molecular Mechanisms of Tissue Growth and Differentiation, Dr. Katyal and Michalopoulos, Director. 2 hrs, Direct Mitogens; Chemical-Induced Liver Regeneration (2000 -2009) and The Placenta (2005-2009).
Stem Cells, S.P. Monga, Director, one and a half hrs, Hepatocytes from Nontraditional Sources. 2002- 2005.

Course Director, Cellular Therapy, MSCMP 3770 and BOENG 3770, Summer session. 6.0 hrs lecture, General Principles and Hepatocyte Transplantation,. (2005-2009)

In House Grant Reviewer, IMRF (1994-
Graduate Recruitment Committee, 2002-2003
Invention Review, Technology Transfer Office, 1998, 1999, 2001,2005,2007.
Embryonic Stem Cell Research Oversight (ESCRO) committee 2006 -

Teaching (Pittsburgh Only)
Member, Graduate Faculty
Advisor, Graduate Students, Minji Jo, Mara Molitor, Ph.D program
Advisor, Medical Student, K.K.Y. Lai,Research Year, 1997-1998. Elective, 12 weeks, 1999.
Advisor, Nisha Sambamurthy (rotation, (2008)
Advisor, Brian Sicari, (rotation 2008)
Advisor, Marc Hansel (rotation, 2008)
Advisor, Qian Sun (Katie) (Rotation, 2008)
Advisor, Graduate Student, MarC Hansel, Pathology, (2009 -)

Dissertation Committee Member
Yingze Zang, Pathology 1997-1998
Dai-Wu Seol, Pathology, 1997-1998
Jie-Gen Jiang, Pathology, 1997-1999
Tae-Hyung Kim, Pathology, 1998-1999
Aaron Bell. Pathology, 1998-1999
Vinod Ramachandran, Pharmacy, 1999-2001
Peter Pediaditakis, Pathology, 1998-2001.
Angela Glading, Pathology, 2000-2002
Yongee Zhao, Pathology, 2002-2004
Hui Tan, Pharmacy, 2003-2005
Zheda Khan, Pathology, 2003-2005
Vladimire Sandulach, 2004- 2006
Bernard Komoroski, Pharmacy, 2003 - 2005
Aarati Ranade, Pharmacy 2004- 2006
Xin He, Department of Pathology 2006 – 2008 (10/26/07, 3/24/08)
Eric Tatro, Department of Pathology, 2006 – 2008) (10/17/07, 4/15/08)
Kristen Skvorak,, Cell and Molecular Biology.2006 – 2008
Tiffany Sellaro Biomedical Engineering, 2006 – 2008
Shringi Sharma, School of Pharmacy 2006- (12/20/07 – 11/2009)
Lauren Drowley, Biomedical Engineering, 2007 – 2009.
Yvonne Chao, MD, PhD Program (2008 -)
Kari Nejak-Bowen (2008 -)
Rohan Manohar, (2008 -)
Nissanne Ghonem, School of Pharmacy, (2008 -)
Ian Bahr, Biomedical Engineering (2008 -).
Sarah Beckman, Pathology, 2009 -

Research Associates and Postdoctoral Fellows
Vsevolod Kostrubsky, Ph.D. 1997-1999, Drug Metabolism with Human Hepatocytes
Hongbo Cai, MD, Ph.D., 9/99 – 2006 Hepatocyte Transplantation, Hepatocyte Culture Models
Fumiaki Nakazawa, MD, Ph.D.10/99 –2001Hepatocyte Transplantation, Animal Models.
Thomas Lehman, Ph.D. 2003- 2006 , Optimizing Human Hepatocyte Cultures
Toshio Miki, MD, Ph.D., 10/01- 2006, Stem Cell Biology
Ewa Ellis, Ph.D. 2004 – 2008. Human Hepatocyte Isolation Transplantation
Keitaro Mitamura, MD, 2005 – 2/2007 (Surgeon), Human Hepatocyte Isolation and Transplantation.
Aarati Ranade, 2006 – Drug metabolism with human hepatocytes and hepatocyte-derived stem cells.
Fabio Marongiu, 2006- 2009, Differentiation of amniotic stem cells to hepatocytes, transplantation.
Roberto Gramignoli, 2007 -2009

Veysel Tahan 8/1/08 –
Summary, Dr. Strom as Primary Mentor for MS and Ph.D candidate students, all sites.

Zahra Salehi, M.S., Duke University
John Faust, Ph.D, Duke University
Sharon Presnell, Ph.D., Virginia Commonwealth University
Maura Molitor, M.S., University of Pittsburgh
Minji Jo, Ph.D., University of Pittsburgh
Marc Hansel, Ph.D candidate, University of Pittsburgh (current)

RESEARCH

Active Grant Support Current Year

Grant Title:	RC1 DK 086135-01, Mice humanized with hepatocytes and iPS cells from patients with metabolic disease.	
Source:	NIH / NIDDK,	
P.I.	Stephen Strom, 25% Effort	
Years inclusive:	10/1/2009 – 9/31/2011	
2-year support:	Direct:	$ 650,000
	Indirect:	$ 340,000
	Total	**$ 980,000**

The goals of this application are to humanize the liver of special immunodeficient mice (FRG, deficient in FAH, RAG-2 and the common Gamma chain of IL2 receptor) by transplantation with human hepatocytes and iPS cells (induced to differentiate to hepatocytes), from patients with metabolic liver disease. The diseases under study are OTC deficiency, and Progressive familial intrahepatic cholestasis (PFIC-2, the BSEP defect) and possibly Crigler-Najjar. The mouse models for these diseases do not reflect the phenotype or the severity observed in human patients. Thus, we will try to recreate the human disease by repopulation of the FRG mouse with metabolic disease hepatocytes and iPS cells generated from hepatocytes or fibroblasts, that have been induced to differentiate to hepatocytes in culture. In addition, we propose to attempt to correct genetic defect in the mutant iPS cells by methods such as homologous recombination or gene transduction. Thus, in the future, a patient might be able to receive an autotransplant of his corrected hepatocytes to correct the metabolic liver disease.

Grant Title:	Liver Tissue and Cell Distribution System (LTCDS)	
Source:	NIH / NIDDK, Multicenter GrantAward	
P.I.	Harvey Sharp,	
P.I.	University of Pittsburgh, Stephen Strom, 5% Effort	
Years inclusive:	02/01/99 – 3/31/2011	
Current Year:	Direct:	$ 121,711
	Indirect:	$ 50,359
	Total	**$ 151,077**

This is a multicenter award from NIH/NIDDK that provides partial support to supply human hepatocytes and human liver tissue to other NIH-funded investigators. Dr. Strom is the Director of the program for hepatocytes and normal liver. Diseased liver is obtained from other labs. The Strom lab is the national center for distribution of normal human liver and isolated (normal) human hepatocytes.

Grant Title	Regulation of drug metabolizing enzyme ontogeny	
Source:	NIH/ R01 GM081344	
PI:	Ronald Hines, Medical College of Wisconsin	
PI:	University of Pittsburgh, Stephen Strom	
Inclusive Dates:	3/1/09 -2/28/2013	
Costs	Direct	$105.753
	Indirect	$ 53,934
	Total	**159,687**

The goals of this research are to follow the maturation of the human liver drug metabolizing enzymes in culture and, *In Vivo*. We use chromatin IP procedures to identify genes and transcription factor pathways activated at different stages in differentiation of the human fetal and neonatal liver. Since the fetal hepatocytes show only modest levels of maturation in culture (to date), in addition to the in vitro experiments, we transplant the fetal cells into the liver of mice and follow maturation of the human cells, *in vivo*. Human fetal hepatocytes, from mid gestation liver show slow approximately 75-80% maturation to the adult phenotype over 6 months post transplantation into the mouse liver.

Grant Title:	Pharmacogenetics of Anticancer Agents	
Source :	NIH/NCI, U01 Multicenter Grant	
PI:	Mark Ratain, Univ.Chicago,	
PI:	University of Pittsburgh, Stephen Strom, (25%)	
Years Inclusive:	4/1/00 - renewed 6/30/05 - 6/2010	
Current Year:	Direct	$ 94,558
	Indirect	$ 48,224
	Total	**$ 142,782**

The Strom laboratory is part of this multicenter study and serves as the normal liver bank for these studies and our laboratory isolates and cultures human hepatocytes and conducts drug metabolism and induction experiments with cultured cells to obtain genotype/phenotype information on drug metabolizing pathways in human liver.

Grant Title:	Hepatic differentiation of placenta-derived stem cells for toxicology	
Source:	Pfizer	
P.I.:	Stephen Strom (15%)	
Inclusive Dates:	1/1/08 – 12/31/09	
Costs:	Direct	$ 245,854 (2 years)
	Indirect	$ 135,220
	Total	**$ 381,074**

In these studies, we examine different stem cell sources to produce functional hepatocytes for pharmaceutical research. We focus on amnion-derived stem cells and induced pluripotent stem cells (iPS) generated from human amnion epithelial cells, human fibroblasts and normal (and diseased) human liver.

Grant Title	Studies of Hepatocellular Cancer in humanized mouse models.
Source	Vertex Pharmaceuticals
Co-PI	Stephen Strom
Inclusive Dates	2010 – 2012,

Costs	Direct	$ 130,000
	Indirect	$ $66,300
	Total	**$ $196, 300**

Human hepatocellular carcinoma (HCC) does not routinely engraft and proliferate well following xenotransplantation into immunodeficient mice. We propose that the human liver microenvironment is critical to xenograft survival and function. We propose to humanize the liver of immunodeficient mice and isolate and transplant primary HCC (not cultured cell lines) to develop and optimize this model for HCC research and use it to test the efficacy and toxicity of new drug entities.

Research Related Activities

Study Sections/Ad. Hoc Reviewer of Research Proposals

Environmental Protection Agency, July, 1984, Principal researcher and author of US Environmental Protection Agency, (EPA) summary finding on Ozone Toxicity.
Pew Foundation. Reviewer of Research Grants, January, 1985
National Institute of Environmental Health Sciences (NIEHS) Review of Research Grants 1-2 times per year, 1984, 1985. 1986.1987, 1993
National Institutes of Health, 1987; 1992
NCI-CSSG Review Committee Member Oct. 1992
American Cancer Society
Cell and Developmental Biology Committee (Study Section), 1989-1990
Personnel for Research, Section C, 1991-1993
Vetrens Administration Medical Center Merit Reviews, 1993
National Institutes of Health, Bethesda Md (NIH)
NIAAA, Alcohol and Toxicology Study Section, 1999
Surgery, Anesthesiology and Trauma (SAT), 2000
NIAAA, Alcohol and Toxicology Study Section, Feb. 2006
NIAAA ZAA1 DD (72) Alcohol Metabolism and Epigenetic Effects on Tissue Injury July 24-25, 2006
NIH, ZRG DIG –E 10B Digestive Sciences and Bioengineering Special Emphasis Panel, Nov 15, 2007
NIH ZRG1 DKUS –B 02 M, Special Emphasis Panel, January 16, 2009
NIAAA, ZRG1 Dig-E, JJ45-1, Special Emphasis Panel, May 5 2009
NIH/NIAAA RC 2009, June 2009.
NIH/ NCI Tumor Microenvironment (TME), June 14-15, 2010

California Inst. for Regenerative Medicine (CIRM)

April 2008,	RFA 07-04, Disease Team Planning Awards
	RFA 07-05, New Cell Lines
Sept. 9-10, 2008,	RFA, 08-02, Tools and Technology
Feb 9-11, 2009	RFA 08-05, Early Translations

Grant applications from Netherlands,(2001) and Italy, 2002
Israeli Scientific Foundation (ISF), 2003 and 2004
UK, Wellcome Trust, 2003, 2004, 2005, 2006, 2007, 1/2008
Cancer Research, UK, 2005,

German Federal Ministry for Education and Research, Cell based regenerative medicine, Bundesministerium fur Bildung and Forschung, Forderprogram Zellbasierte, Regenerative Medizin (BMBF 612-71470-2, (2005)
German Federal Ministry of Education (BMBF) "Cell based regenerative medicine, Berlin Germany, August ,2008)
Fonds De La Rechierche Scientific-FNRS, (Medicale)Bruxelles, Belgium (1/2009)
KWF Kankerbestrijding (Dutch Cancer Society) Delflandlaan, Amsterdam, September 09
Dutch Digestive Foundation, July 2010

Journal Reviewer:

Cancer Research
Molecular Pharmacology
Toxicology Letters
Chem-Biol Interactions
Environmental Mutagenesis
Carcinogenesis
Differentiation
J. Cell Physiol
Biochemistry
In Vitro
American J. Pathol.
Molecular Carcinogenesis.
International J. Cancer.
Transplantation
Europ. J. Biochem
Nature Biotechnology
Genes and Development
Toxicology and Applied Pharmacology
Cell Transplantation
Surgery
J. Hepatology
Drug Metabolism and Disposition
Molecular Pharmacology
Transplantation
Liver Transplantation
Genes and Development
Cytotherapy
Proc. Natl Acad. Sciences
Hepatology
Gastroenterology
Nature Medicine

Editorial Board

In Vitro Cell Growth and Differentiation (1998 -)
Cell Transplantation (1998 -)
Cell Transplantation, Section Editor for Hepatocytes (2000 -)
Chinese Journal of Surgery (2003 -)
World Journal of Hepatology (2009 -)
Liver Disease Review Letters (2009 -)

Professional Societies

American.Association for Advancement of. Science
Cell Transplantation Society 1995-2009
American Association Study of Liver Disease 1995- 2009
International Society for Stem Cell Research. 2003 -2009
American Society for Investigative Pathology (ASIP), one of the FASEB societies 2007.
President Elect, Cell Transplantation Society, 2009-2011

INVITED PRESENTATIONS

1978-1993

Michigan State University, Carcinogenesis Laboratory, 1978
American Health Foundation, Naylor Dana Institute for Disease Prevention, 1978.
University of Minnesota, Duluth, Department of Pharmacology, 1982.
University of Alabama, Birmingham, Cancer Center-Pharmacology, 1982.
Duke University, Department of Pharmacology, 1982.
N.I.H.,Bethesda, MD, Oncogene Activation and Hepatocarcinogenesis Conference on Regulation of Growth and Differentiation Normal, Regenerative and Neoplastic Hepatocytes, Nov. 6-7, 1986.
National Inst. Environ. Health Sciences Symposium on Basic Research in Risk Assessment, Research Triangle Park, NC, March 9-12, 1987.
Title: Can In Vitro Studies Assist Us in Species Extrapolation.
Duke University Toxicology Program, 9/7/87
Title: Interspecies Extrapolation of Carcinogenic Risk
Lavale University, School of Pharmacy, Quebec, Canada, 9/15/87
Title: Genotoxicity Studies with Human Hepatocytes.
Lavale University, Cancer Center, Quebec, Canada, 9/16/87
Title: Activated Oncogenes in Hepatocarcinogenesis.
West Virginia University, Department of Pharmacology, 10/6/87
Title: Activated Oncogenes in Hepatocarcinogenesis.
FASEB Summer Research Conference, Neoplastic Transformation of Liver Cells, Copper Mountain, CO International Symposium August 14-19, 1988.
Title: Transformation of Liver Cells With Oncogenes
Symposium on the Pathobiology of Neoplasia, Richmond, VA
April 27-28, 1989. Title: Activated Oncogenes in Hepatic Neoplasia
Normal and Neoplastic Growth in Hepatology: Interface Between Basic and Clinical Science, International Symposium June 21-24, 1989, Pugnochiuso-Foggia, Italy
Title: Transformation of Liver Cells with Oncogenes.
Eli Lilly, Toxicology Division, Transformation of Liver Cells With Oncogenes
February, 1990
FASEB Summer Research Conference Hepatic Regeneration and Carcinogenesis: Molecular and Cellular Pathways, July 30 - Aug. 3, 1990 Copper Mountain, CO.
Title: Transformation of liver epithelial cells with an expression vector for rat transforming growth factor-α: Complementation with c-myc.
National Disease Research Interchange, Third International Conference Sept 16-18, 1990 Washington, D.C. Title: The use of human hepatocytes for studies of genetic toxicology.
FASEB Summer Research Conference Hepatic Regeneration and Carcinogenesis: Molecular and Cellular Pathways, July 12-17, 1992 Snowmass, CO.
Title: Simian Virus 40 Immortalization of Human Hepatocytes.
American Cyanamid Research Laboratories, Nov, 1992. Xenobiotic and Drug Metabolizing Enzymes in Human Hepatocytes.
NIH, Laboratory of Experimental Carcinogenesis Dec. 4, 1992, Immortalization and Transformation of Human Hepatocytes.
University of Pittsburgh, Department of Pathology, Dec 17, 1992, Use of Human Hepatocytes for Carcinogenesis Research.
Johns Hopkins School of Hygiene and Public Health, Jan 12, 1993, The Use of HumanHepatocytes in Carcinogenesis Research.
University of Pittsburgh Cancer Center, March 11, 1993, Molecular Mechanisms of Hepatocarcinogenesis.

University of Colorado Liver Research Center, April 15, 1993, The Use of Human Hepatocytes in Basic and Clinical Research.
International Symposium, Pathobiology of Neoplasia, Richmond, VA, April 21, 1993, Hepatocyte Transplantation Sustains Life in Acute Liver Failure

1994

NIH, Laboratory of Experimental Carcinogenesis, 1994, Use of Human Hepatocytes in Basic and Clinical Research.
Albert Einstein College of Medicine, Liver Research Center, Bronx, NY, February 1994 Human Hepatocyte Transplantation Supports Life in Terminal Liver Failure.
FASEB Symposium, Anaheim, CA, 1994 , Induction of Xenobiotic Metabolism and Cytochrome P450 Genes in Human Hepatocytes.
FASEB Summer Conferences, Hepatic Regeneration, August 1994, Transplantation of Human Hepatocytes Supports Life in Terminal Liver Failure, Copper MT, CO

1995

FASEB Conference, Prostate Biology and Neoplasia, January 17, 1995 Palm Springs, CA Growth Factor Requirements of Human Prostate Epithelial Cells,
Society of Toxicology, March 7, 1995, Baltimore, MD, Regulation of Human Cytochrome P450-genes in Human Hepatocytes. Special Symposia on the Use of Human Organs and Tissues in Research.
Schering-Plough, Kenilworth, NJ, March 1995, The Use of Human Hepatocytes in Basic and Clinical Research..

Park-Davis, Ann Arbor, MI, April 10, 1995, The Use of Human Hepatocytes in Basic and Clinical Research
Gift of Life Organ Procurement Agency of Michigan, Continuing Education Series, April 11, 1995 Hepatocyte Transplantation Supports Life in Terminal Liver Failure
Isis Pharmaceuticals, Carlsbad, CA, Human Hepatocytes in Toxicology Testing and Drug Development, August 16, 1995
Transplant Resource Ctr of MD, Baltimore, Human Hepatocyte Transplantation. Oct. 13, 1995
St. Louis University Health Sciences Center, Department of Pharmacology, Human Hepatocytes n Basic and Clinical Studies, October 19, 1995.
American Health Foundation, White Planes N.Y., Human Hepatocytes in Basic and Clinical Research, October 25, 1995.
Southwest Transplantation Conference, Las Cruces, New Mexico, Nov 4, 1995, Human Hepatocyte Transplantation.
University of Georgia, Department of Surgery, Grand Rounds, Nov. 17, 1995, Human Hepatocyte Transplantation.
NIH, Bethesda, MD., Hepatic Stem Cells, December 9, 1995. "The Role of C-kit and Stem Cell Factor in Human Hepatic Diseases".

1996

Burlington, VT, Keystone Conferences, Hepatitis C and Beyond January 23-29, 1996, "Isolation, Culture and Infection of Human Hepatocytes With Hepatitis C.
Southwest Organ Bank, Dallas Texas and Baylor Medical Center, Department of Transplantation Surgery and 2/27/96, Human Hepatocyte Transplantation.
Schering-Plough Research Inst. Kenilworth, NJ, 3/21/96, Mouse/Human Chimeric Models for Hepatitis C.

Medical College of Georgia, Regional Meeting, Organ Transplantation, Present and Future. Human Hepatocyte Transplantation, March 23, 1996 Savanna, Georgia.
Medical College of Virginia, Richmond, VA, Department of Pharmacology, "Human Hepatocytes in Basic and Clinical Studies", and "Investigation of Drug Metabolism with Human Hepatocytes" , April 29, 1996.
University of Nebraska, Department of Transplant Surgery, Omaha, NE May 2, 1996 "Human Hepatocyte Transplantation"
American Society for Artificial Organs, National Meeting, May 4, 1996, Washington Hilton, Washington, DC, Session on Liver Assist Devices, Human Hepatocyte Transplantation.
Baylor Medical Center, Department of Transplantation Surgery, June 13, 1996 Human Hepatocyte Transplantation.
North American Transplant Coordinators Organization (NATCO), Annual Meeting, August 5, 1996, " Bridging to Transplantation" ," Human Hepatocyte Transplantation"
FASEB Summer Conferences, Hepatic Regeneration, Snow Mass CO. August 6, 1996 Isolation Culture and Infection of Human Hepatocytes with Hepatitis C.
INSERM, Institut National, de la Sante et de la Rechererche Medicale, Meeting "Therapeutic Use of Hepatocytes and Pancreatic Islets"Human Hepatocyte Transplant, Nov.15-17,1996.
BIOWHITTAKER Walkersville, MD, Transplantation of Human Hepatocytes, December 15, 1996.

1997

University of California, San Francisco, Department of Transplantation Surgery, Human Hepatocyte Transplantation, January 15, 1997.
Starzl Transplant Institute, University of Pittsburgh, Feb. 10, Human Hepatocyte Transplantation.
Clonetics, Corp. San Diego CA. April 11, 1997 Transplantation of Human Hepatocytes.
Boston University, Department of Gastroenterology, Boston MA, and Diacrin Inc. Transplantation of Human Hepatocytes.
South West Organ Procurement Agency, Coordinators Regional Meeting, Dallas, TX. Human Hepatocyte Transplantation, June 19, 1997.
University of Kansas Medical Center, Kansas City ,KS, Dept. of Pharmacology. August 27-28, The Use of Human Hepatocytes for Basic and Clinical Studies.
International Symposium on Culture Systems for Hepatitis Research. Schering Plough Research Institute, Kenelworth, NJ. Nov. 12. Studies of Hepatitis C with Human Hepatocytes.
Society for In Vitro Biology, Regional Meeting and Food and Drug Administration Intercenter Tissue Engeneering Working Group, Laurel MD. November 18. Human Hepatocyte Transplantation.
Glaxo-Wellcome, Ware, England, Dec. 2, The Use of Human Hepatocytes for Basic and Clinical Studies.
SmithKline-Beecham, The Fryth, Welwyn, Hertfordshire, England, Dec. 3, The Use of Human Hepatocytes for Basic and Clinical Studies.
Zenica Pharmaceuticals, Manchester, England. Dec. 4, The Use of Human Hepatocytes for Basic and Clinical Studies.
Chiron Corporation, Emmeryville CA. Dec. 18-19, Human Hepatocytes as a Model System for Hepatitis C Research.

1998

Schering-Plough Research Inst. Kenelworth, New Jersey, February. 10, 1998 A Novel, In Vivo, Model for Hepatitis Research.
Abbott Pharmaceuticals, Abbott Park, IL, March 13, 2 Seminars "The Use of Human Hepatocytes

for Basic and Clinical Studies", and "In Vitro Investigations of Hepatitis C".
University of Pittsburgh, Dept. Pharmacology, April 24, The Use of Human Hepatocytes for Basic and Clinical Studies.
University of Washington, Seattle, Center for Ecogenetics and Environmental Health, April 29, The Use of Human Hepatocytes for Basic and Clinical Studies.
Pharmacia and Upjohn, Kalamazoo, MI, Infectious Diseases, May 5, "The Use of Human Hepatocytes for Basic and Clinical Studies" and "In Vitro Studies of Hepatitis C"
King's College Hospital, London England, 2 Biennial Alex Mowat Pediatric Hepatology Update June 1+2, 1998, "Human Hepatocyte Transplantation-Technical Aspects"
Bristol Meyers-Squibb, Wallingford CT. June 10, 2-seminars, The Use of Human Hepatocytes for Basic and Clinical Studies and In Vitro Investigations of Hepatitis C.

Eli Lilly Indianapolis IN Human Hepatocytes is basic and clinical research. and In Vitro investigations with Hepatitis C Virus., June 17-18, 1998
University of Chicago, Department of Surgery, Division of Transplantation, June 26, Human Hepatocyte Transplantation.
International Conference, Choice of Cell Lines for High-Throughput Screening, Aug 13-14, 1998 "Cultured Human Hepatocytes for Pharmaceutical Research" San Diego,CA.

1999

Chiron, Corp. Emmeryville, CA, *Human Hepatocyte Models for Hepatitis C*. Jan 19-21, 1999.
Regenerative Technologies, Gainsville, FL. *Human Hepatocyte Transplantation*, Jan 24-25, 1999
Glaxo-Wellcome, Research Triangle Park, NC, Feb. 17-18, 1999. *The Use of Human Hepatocytes in Drug Metabolism and Hepatitis Research.*
Encell, Inc. Greenville, NC. *Human Hepatocyte Transplantation*. April 12-13, 1999.
TestSmart – A Humane and Efficient Approach to SIDS Data, Workshop, Alexandria Virginia, April 26-27. *Human Hepatocytes for Drug Metabolism and Toxicity Testing*
Academy of Cllinical Laboratory Physicians & Scientists, 1999 Annual Meeting, Birmingham, AL, June 3- 5, 1999. *Human Hepatocyte Transplantation*
Society for In Vitro Biology, New Orleans, LA, June 5-7, *Human Hepatocyte Transplantation.*
Hoffmann LaRoche, Nurtley, NJ, August 5-6,
The Use of Human Hepatocytes in Basic and Clinical Research
Am Assn. Tissue Banks, Annual Meeting, San Diego, CA, 8/20-22, Human Hepatocyte Transplantation.
Parke-Davis, Ann Arbor, MI 8/23-24. *The Use of Human Hepatocytes in Basic and Clinical Research*
Cagliari, Sardinia, Italy, Oct.5-7, 1999. Intl. Conference on "Therapeutic Liver Repopulation" *Human Hepatocyte Transplantation.*
AASLD, Dallas Texas, Early Morning Workshop, Nov 5-9, 1999. *Hepatocyte Transplantation*
NIH, Bethesda, MD, Stem Cell Meeting. *Use of Fetal Hepatocytes for Clinical Transplants.* Dec 10, 1999
Brown University/ Rhhode Island Hospital, *Human Hepatocyte Transplantation*. Dec 21, 1999

2000

Geron, Inc. SF,CA. *Human Hepatocytes in Basic and Clinical Studies*, Feb. 1-2.
Schering Plough, Kenilworth, NJ, *In Vitro Models for HCV*. March 16-17

Smith-Kline Beecham, King of Prussia, PA, *In Vitro Models of HCV*, April 2-3.
Am Soc. Invest. Path. FASEB, SanDiego, CA, April 15, 2000 *Human Hepatocytes for Clinical Transplants*
Immunex, Seattle, CA, May 9-10, *TRAIL-Induced Apoptosis in Human Hepatocytes*.
Bayer Pharmaceuticals, The Use of Human Hepatocytes for Basic and Clinical Uses.
8th International TNF Congress. Trondheim, Norway, May 14-19. *TRAIL-Induced Hepatocyte Apoptosis*. Chair, 2 sessions on TNF-Defense and Disease, May 16, 17.
Pfizer, Groton CT. June 26-27. *Use of Human Hepatocytes in Basic and Clinical Studies.*
International Workshop on Hepatocyte Transplantation, London, UK, June 29
June 30, Seminar: Human Hepatocyte Transplantation, King's College University, London
Gordon Conference, Drug Metabolism, July 9-14, 2000. *Modeling Human Hepatic Function, In Vitro*

FASEB Summer Conference Mechanisms of Liver Growth and Differentiation in Health and Diseases *Human Hepatocyte Isolation and Transplantation* Snowmass, CO, July 29-Aug 3, 2000.
Merc and Company, August 14-15, The Use of Human Hepatocytes for Basic and Clinical Studies. University of Chicago August 17-18.
Dept Clinical Pharmacology. The Use of Human Hepatocytes for Basic and Clinical Studies, Dept. Surgery Human Hepatocyte Transplantation.
Am Assoc Study of Liver Disease (AASLD) Presenter, Early Morning Workshop #311, "Hepatocyte Transplantation", Oct 29. 2000.
International Conference "Therapeutic Use of Human Cells", Padua, Italy, Nov 29-Dec.3, 2000 Human Hepatocyte Isolation and Transplantation

2001

Pittsburgh Cancer Institute, Cancer Consortium, Pittsburgh, PA 2/24/01, Trail Toxicity to Human Hepatocytes
Human Genome Sciences, Rockville, MD, Trail Toxicity Towards Human Hepatocytes, 3/27/01
Alabama Organ Center, Birmingham, AL. In Service Lecture Human Hepatocyte Transplantation 4/26/01.
UNOS Area 6 Meeting, Portland OR, 5/3/01, In Service Lecture: Hepatocyte Transplantation.
Merck and Co., Philadelphia, PA, "Use of human hepatocytes for hepatitis research"
Moorehouse School of Medicine, May 7 – 12, 2001, Wellcome Visiting Professor
Dept. of Pharmacology, May 8, Investigating Drug Metabolism with Human Hepatocytes.
Surgery Grand Rounds, May 9, Human Hepatocyte Transplantation.
New England Drug Metabolism Group, Wocester, MA, May 13 Invited Lecture
"Use of Human Hepatocytes for Drug Metabolism Studies"
Intl. Liver Transplantation Society Meeting, Berlin, Germany, July 11-13,
"Fetal Human Hepatocytes for Clinical Transplants"
NIH/NIAAA, Dr. Bin Gao, Lecture, "The use of human hepatocytes in basic and clinical studies" Sept 6, 2001
Indiana Organ Procurement Org. (IOPO) In Service Lecture: Human Hepatocyte Transplantation
Falk Symposia, No 124-126, Progress ion Gastroenterology and Hepatology, 2001, Sept 28- Oct 3 Hanover Germany, "Hepatocyte Isolation for Clinical Transplants".
Cell Transplantation Society Meeting, Keystone, CO.
Director, Hepatocyte Program and Speaker,
Oct 14-17, "Fetal Human Hepatocytes for Clinical Transplants"

Organ Donor Services, Salt Lake City, Utah, October 18 "Hepatocyte Transplantation"
Nevada Donor Network, Las Vegas, NV In Service Lecture Oct. 19 "Hepatocyte Transplantation"
Am Assoc Pharmaceutical Sciences, Invited Lecture, Human Hepatocytes in Drug Metabolism Studies Oct 23, Denver CO.
Am Assoc Study of Liver Disease (AASLD) Invited Speaker, Early Morning Workshop, "Hepatocyte Transplantation".
Southern California Organ Donor Services, In Service Lecture "Hepatocyte Transplantation" San Diego, CA Nov. 14.
Los Angeles Donor Services, LA,CA, Nov. 15 In Service Lecture" Hepatocyte Transplantation" Pharmacia, St. Louis, MO, Drug Metabolism Nov 19, Drug Metabolism Studies with Human Hepatocytes.

2002

Use of Human Hepatocytes to study Drug Metabolism, Strategic Research Institute Conference, Philadelphia, PA March 5
Transplantation of Human Hepatocytes, Gift of Life, Hartford CT. March 14
Transplantation of Human Hepatocytes, Organ Procurement Agency, Seattle WA, March 18
International Meeting of the Pediatric Transplantation Society, Rio deJaniero, Brazil "Human Hepatocyte Transplantation" (Meeting Cancelled because of Terror Concerns)
Alpha-1 Foundation, Stem Cells and New Therapies, Miami Fla, April 17-20."Human Hepatocyte Transplantation".
Midwest Toxicology Society, May 16-17, Drug metabolism studies with human hepatocytes.
AASLD Single Topic Conference, Airlie VA June 7-9, "Human Hepatocyte Transplantation".
Center for In Vitro Sciences, June 19, "Toxicology studies with human hepatocytes"
IOPA, Iowa City, Iowa July 17, "Transplantation of human hepatocytes"
Albany NY, Organ Procurement Agency, "Human hepatocyte transplantation", Sept. 24
Regenerative Medicine Inst., Washington DC, Dec 3, "Human hepatocyte transplantation".
Predictive Toxicology, Philadelphia, PA December 11, "Toxicology studies with human hepatocytes"

2003

Magee Women's Res. Inst. Placental Stem Cells, Jan 31, 2003
Pharmacia, Kalamazoo, MI, February 19, "Humanizing mouse livers with human hepatocytes"
International Meeting of the Cell Transplantation Society; Atlanta, Ga. March 4, "Cell transplantation; hepatocytes to stem cells, plus Chair 2 sessions.
Society of Toxicology, Salt Lake City, UT. March 10 Symposium, Use and application of stem cells in toxicology, Title: "Hepatocytes from Stem Cells"
Engineering Tissue Growth, Intl Conference, Pittsburgh, Pa, March 21, "Cell Therapy for Liver Disease"
Aventis Phamaceuticals, Bridgewater, NJ, April 2, "Toxicology studies with human hepatocytes"
Crigler-Najjar Assn. Lancaster, PA. Annual meeting June 11-12,Title: Human Hepatocyte Transplantation
Liver Proteome, NIH, Bethesda Md. July 17-18, Banking of Human Liver Tissue and Isolated Cells.
Toxicity of Herbal Products, NIH, Bethesda, MD. Sept 8-9, Title Studies of Herbal Products with Human Hepatocytes.
Iowa Donor Network, Annual Meeting, DesMoines Iowa, Sept 18-19, Transplantation of Human Hepatocytes.
Ohio State University, Columbus, Surgery Grand Rounds, Oct 8. "Human hepatocyte

transplantation"

Pfizer Global Research, Grotton CT. Oct 16, Pluripotent Stem Cells from Placenta.

AASLD, Boston Annual Meeting, Chair Session "Cellular Therapy", Oct. (26.3-4PM).

University of Utah, Salt Lake City, Dec 1. "Cell Transplantation: From Hepatocytes to Stem Cells"

Northeastern Ohio Univ.Medical School, Rootstown, OH. Biochemistry, Dec 10. "Studies with Human Hepatocytes"

2004

Penn. State Univ. Jan 21, Center for molecular toxicology and carcinogenesis, "Cell Transplantation: From Hepatocytes to Stem Cells"

Intl. Society Study of Xenobiotics (ISSX), Vancouver, BC Satellite Meeting, Hepatocyte Users Group, Human Hepatocytes, Optimization of culture conditions. August 28, 2004.

Georgetown University, Department of Gastroenterology, Grand Rounds, Hepatocyte Transplantation., September 1, 2004.

NIH/NIDDK, (John Tisdale) Stem Cell Derived Hepatocytes., Sept. 2, 2004

Intl. Congress of the Transplantation Society, Vienna, Austria, Sept 5-10, "New Directions in Hepatocyte Transplantation"Sept 7.

Intl. Cell Transplantation Meeting, Boston, MA November 17-20, 2004., Director Hepatocyte Sessions, Chair, Hepatocyte Transplantation Session, Presentation Cell Transplantation, from hepatocytes to stem cells.

Novartis Pharmaceuticals, Advisior Board. "Perspectives in Cell Therapy with Hepatocytes", November 19, 2004, Boston MA..

2005

Third International Symposium on Hepatic Failure and Artificial Liver. March 24-27, Suzhou, P.R. China, Presentation, Heptocyte transplantation for the treatment of liver disease.

Virginia Commonwealth University, Richmond, VA, Department of Pathology, April 15. Cell Transplantation, from hepatocytes to stem cells.

University of Rome, La Sapienze, Department of Surgery, April 18.(or 24) Hepatocyte Transplantation.

Meeting on Regenerative Medicine and Artificial Organs, April 20-22, 2005, Polermo, Italy, Presentation, Hepatocyte transplantation for the treatment of liver disease.

European Society for Pediatric Gastroenterology, Hepatology and Nutrition. Porto, Portugal, June 1-5. Presentation, Large scale isolation of human hepatocytes for transplantation, past, present, future.

Expert Workshop on Stem Cell-Derived Hepatocytes, July 7-8, Frezenious, Inc. Frankfort, Germany. Title Placental Stem Cells.

Showa University International Life Science Symposia, Sept 17, Tokyo, Japan, Title Human Hepatocyte Transplantation for Liver Disease.

2006

Alpha 1 Foundation single topic conference, Alpha-1-antitrypsin deficiency and other liver diseases caused by aggregated proteins. Emery conference center, Atlanta, Ga, Jan. 26-28., Session, Novel therapies, presentation, Hepatocyte Transplantation.

Department of Hepatology, Hannover Medical School, Hannover Germany, Stem Cell Derived Hepatocytes. January 17, 2006.

Cytonet, Hannover Germany, January 18, 2006. Title: Hepatocyte Transplantation.

University of Kansas Medical Center., Kansas City Kansas. March 14, 2006, Title: Hepatocyte transplantation from hepatocytes to stem cells.

Cell Transplantation Society, International Meeting, Milano, Italy, May 19-21, 2006
Human heptocyte transplantation.

Japanese Society for Research on Hepatic Stem Cells, June 30-July 1, 2006, Asahikawa, Hokkaido, Japan. Title, Human hepatocyte transplantation for liver disease.

Pfizer Global, Groton CT, Amnion –derived Stem Cells, Potential uses for Toxicology.

World Transplant Congress, Boston MA, July 22-27, 2006. Hepatocyte Transplantation for Metabolic disease. (July 27).

Valencia, Spain, November 4, 2006. Hepatocyte Transplantation, an Overview.

2007

Hepatic Failure and Artificial Liver, Chongqing, PR China, Hepatocyte Transplantation, March 9-12, 2007.

CK, Ltd. Hong Kong, China. March 15-17, 2007, Title Placental Stem Cells.

1st International Symposium on Regenerative Medicine and adult stem cell. Seoul Korea ans RNL, Ltd. Title: Amnion derived stem cells. March 19-21, 2007.

Placenta derived stem cells, Workshop., March 23-34, 2007. Brescia, Italy. Title Amnion-derived stem cells.

Am. Soc Investigative Pathology (FASEB), May 1, 2007, Wash DC. Title, Placental Stem Cells.

International Study Group for Stem Cell Therapy, Hurghada, Egypt, May 8-11, 2007.. Hepatocyte transplants from liver to stem cells.

Society of Toxicology, Michigan Chapter, Stem Cell Derived Hepatocytes. May 18, 2007

NIH/NIDDK, Conference on Methylmalonic Acidemia (MMA). June 17-19, 2007, Title Hepatocyte transplantation for metabolic liver disease.

Rozman Symposium, Langhorn, PA , May 24, 2007, Cell Transplantation, from hepatocytes to stem cells.

2007 Frontiers in Human Embryonic Stem Cells, Advanced Training Course – Pittsburgh; August 5th - 10th , Lecture: Placental Stem Cells. And demonstration workshop. Aug 10

Cell Transplantation Society, International Meeting, Minneapolis MN. Sept 15-20, 2007, Title, Mature Liver Functions.

Japanese Society of Hepatology, Iwate, Japan Hepatocyte Transplantation Sept 28-29, 2007.

2nd International Symposium on Regenerative Medicine and adult stem cell. Seoul Korea, November 7, 2007.

Carl-Gustav Groth Lecture, Congress of the Swedish Society of Medicine, November 29, 2007. Title: Hepatocyte Transplantation, State of the Art.

2008

International Conference on Stem Cell Research, Yamaguchi University, Japan, Feb 2, 2008, Title Hepatocyte Transplantation.

Falk Symposium # 163, Chronic Inflammation of the liver and Gut, Hang Zhou , P.R.China, March 14 and 15, 2008. Title: Hepatic stem cells: therapeutic options for the future.

CK Biotechnologies, Hong Kong, PRC. March 19, Stem Cell-derived hepatocytes.

New Jersey Drug Metabolism Group, May 7, 2008, The use of human hepatocytes in drug metabolism research.

Study Group for Stem Cell Therapy, Hurghada, Egypt, June 25-28,2008. Hepatocyte transplants from liver to stem cells.

ESH-EHA, Scientific workshop on mesenchymal stem cells, Mandelieu, France, 6/30 – 7/2.

California Inst. Regenerative Medicine, July 7-8, Th use of stem cells in toxicology research.

Vertex Pharmaceuticals, 7/28. Human hepatocytes in drug metabolism studies.

2nd Biennial Intl.Collaborative Symposium on Stem Cell Research, Seoul Korea, Sept 18-19. Stem

Cells from Amnion.
Am. Assoc Blood Banking, Montreal, Canada, Oct 4-7, Human Hepatocyte Transplantation.
Taiwan Intl. Somatic Stem Cell Symposium. Nov. 8, Stem Cells from Amnion.
International Hepatobiliary Surgery Forum, Hunan National University, Changsha, China. Nov. 13-15, Human hepatocyte transplantation to treat liver disease.

2009

International Workship, Placenta-derived cells for the treatment of inflammatory diseases: moving toward clinical application, March 13-14, Foundazione Poliambulanza Instituto Ospedaliero, Brescia Italy, Title, Placental stem cells for regenerative medicine.
Karolinska, Institute and Hospital, March 17, Lecture in Cellular Therapy Course " Placental stem cells for regenerative Medicine"
Lecture # 2, March 19, Hepatocyte Transplantation in a murine model of intermediate Maple Syrup Urine Disease (iMSUD). Department for Clinical Science, Intervention and Technology CLINTEC
American Association of Pharmaceutical Sciences (AAPS) Workshop Drug transporters in ADME from bench to bedside. March 29-April 1, 2009, Sheraton Inner Harbor Hotel, Baltimore. "Stem cell derived hepatocytes and humanized mice, new technology for research (April 1)
Cell Transplantation Society, International Meeting, April 20-21 Okayama Japan, Discussion leader and Chair, Stem cell-derived hepatocytes and mature hepatic function.
TERMIS Tissue engineering and regenerative medicine International Society, August 31-Sept. 3, Lotte Hotel World, Seoul Stem Cell Symposium, Seoul, Korea, Keynote Speech, "Amnion derived stem cells for regenerative medicine". Morning Sept 3.
International Consensus Group Meeting on Hepatocyte Transplantation, Kings College, London Sept 6-7, 2009. Participant, Group Leader, Session 1 Sources of Hepatocytes, In charge of writing the report.
2nd International Liver Symposium-Isparta, Anatala, Turkey, Sept. 24-27, "Hepatocyte transplantation, from stem cells to hepatocytes". Lecture 2, New Tools for liver research, stem cell-derived hepatocytes and humanized mice.
National Meeting of Turkish Society of Gastroenterology, Oct 14-17, 2009, Ankara Turkey. Cell Transplantation, from hepatocytes to stem cells
Stem Cell USA & Regenerative Medical Congress, November 16-18 in Washington D.C.
Hepatocytes from Stem Cells. (Cancelled for Sweden Trip).
Karolinska Institute. Liver-Based Regenerative Medicine., November 14-16
International Study Group for Stem Cell Therapy, 3rd Annual Meeting, Cairo, Egypt, Nov 19-2. Liver-Based Regenerative Medicine.

2010

Karolinska Institute, Stockholm, Sweden, March 9, 14, Lecture and laboratory, Stem Cell Course, Amnion-derived Stem Cells. Seminar, Humanized mice, tools for studying drug metabolism and toxicology.

8th World Congress on Trauma, Shock, Inflammation and Sepsis – TRIS 2010, March 9-13, Munich Germany, Lecture March 11, Liver-Based Regenerative Medicine.

Gordon Conference on Drug Metabolism, July 11-16, Holderness School in Holderness, New Hampshire, US, Title: Humanized mice and stem cell-derived hepatocytes, new tools to study drug metabolism and toxicology

FASEB Summer Research Conference, Liver Growth Injury and metabolism: basic and applied biology conference, August 15-20, 2010.

RESEARCH INTERESTS

Hepatocyte transplantation as a clinical treatment of liver disease.
Expression and the regulation of drug metabolizing enzymes and transporters in human liver.
Regulation of human hepatocyte replication and differentiation
Production of hepatocytes for transplantation from stem or progenitor cells.

Personal Statement

My laboratory investigates human liver biology, pathology and disease. We first modeled liver cancer based on human liver mediated metabolism of chemical carcinogens. These studies lead to our development of methods to isolate human liver cells (hepatocytes). Our studies then included and soon became focused on the regulation of the expression and induction Cytochrome P450 genes, where we collaborated, mainly with the Schuetz laboratory and later with the Omiecinski laboratory and helped define the molecular mechanism responsible for the regulation the expression of CYP3A4 and 3A5, and eventually other PXR or CAR target genes.

In 1992, our use of human hepatocytes took a more clinical direction, when we and concurrently the Mito Group in Japan, became the first groups to transplant human hepatocytes into patients with liver disease. We received the first, Investigative New Drug (IND) approval from the US Food and Drug Administration (FDA) to conduct clinical hepatocyte transplants. My laboratory was the first facility to be approved for the isolation of human hepatocytes for clinical transplants. We soon became the liver cell bank for hepatocyte transplant efforts around the US and supplied cells for patient transplants at 4 medical centers. Our transplant group has transplanted over 25 patients, the largest series to date.

We understand that the limiting factor in the use of hepatocyte transplants as a clinical therapy is the availability of useful cells. Thus, we have begun serious research efforts into trying to generate normal, mature human hepatocytes from adult and fetal stem cells (mainly human amnion and fetal liver) as well as Human Embryonic Stem Cells (hES)and now also Induced Pluripotent Stem Cell (h-iPSC).

Recent new efforts have focused on maintaining our isolation techniques to a GMP level and to identify metabolic assays that will predict human hepatocyte function, and can be completed within 2 hrs of cell isolation. This is necessary to establish "Lot Release Criteria" to evaluate human hepatocytes prior to release for clinical transplants. In addition, we focus on methods to enhance engraftment and proliferation of hepatocytes following transplantation. We use surface markers or other physical characteristics of hepatocytes to identify specific subfractions that might show enhanced engraftment or proliferative potential as compared to the general cell population.

We have identified several roadblocks that prevent a more successful implementation of hepatocyte transplantation. Our laboratory has always been relatively small, usually 4 - 6 people, who are dedicated to the investigation and development of methods to optimize clinical hepatocyte transplantation protocols at every step of the process. We are collaborating with a Biotech company to develop and optimize the use of new FDA-approved enzyme mixtures for liver tissue digestion. We have identified useful short term assays to quickly and accurately predict hepatocyte function prior to transplant. We are investigating and improving methods for short-term cold-storage (24-72hrs) and long-term cryo-storage of human hepatocytes. And finally, we investigate multiple cell sources from stem cells to subfractions of human hepatocytes to try to identify those cells with the highest engraftment and proliferation potential.

SHORT CAREER BIO. (usually sent for introductions for speaking engagements)

Dr. Strom started his research career in the Department of Pharmacology at the University of Kansas Medical Center, Kansas City, where he studied the effects of cancer chemotherapeutic agents on bone marrow colony-forming stem cells.
He understood very quickly that it might be easier to prevent cancer than to cure it so in 1978 he chose to do postdoctoral work at Duke University under George Michalopoulos, a well know researcher in liver regeneration, where he studied chemical carcinogenesis. In order to make the data relevant to humans, Dr. Strom developed techniques to isolate hepatocytes from human liver tissue to identify how human liver cells metabolized chemical carcinogens. Dr. Strom worked at Duke University for a total of 10 years first as a postdoctoral fellow and subsequently as an Assistant Professor.

In 1988 He moved to the Medical College of Virginia, in Richmond Virginia, where he soon made contact with a transplant surgeon, Dr. Robert Fisher, and they began to make plans to transplant hepatocytes into patients to treat liver disease. In late 1991 and 1992, 2 groups of investigators conducted the first clinical trials of human hepatocyte transplantation, Dr. Mito in Japan and Drs. Strom and Fisher in Richmond.

Dr. Strom then Moved to Pittsburgh in 1993 and his laboratory was the first in the US to receive FDA (Food and Drug Administration) approval for the isolation of hepatocytes for clinical transplants. Dr. Strom's laboratory continued to serve as a hepatocyte bank for transplants at 5 different Medical Centers in the US. He and his colleagues have transplanted over 25 patients with different types of liver disease.

Dr. Strom is the Director for Hepatocytes, for a US, National Institute of Health (NIH) NIDDK-funded program to isolate and distribute human hepatocytes for basic science. This program serves as the national bank for normal human liver. They procure human liver and isolate human hepatocytes and distribute them to other NIH-funded scientists throughout the US for research. In approximately 8 years this program has already distributed more then 20,000 plates or flasks of human hepatocytes to researchers throughout the US. They also maintain a frozen bank of approximately 300 human livers that investigators can request normal liver tissue for research purposes.

Dr. Strom has been the Associate Editor for Hepatocytes for the Journal Cell Transplantation since 2000 and is currently the President of the Cell Transplantation Society. He has published over 200 research papers, review articles and book chapters and is currently a Professor in the Department of Pathology, University of Pittsburgh.

Research Plans, Stephen Strom, Ph.D.

My over all goals are to identify methods to improve hepatocyte transplantation as a therapy for liver disease. The 5-year research plan described here is based on the road-blocks I perceive for hepatocyte transplantation and the unmet needs for this field of clinical investigation. To accomplish these goals I will focus on the studies below.

1. Improve the cell sources for transplantation.
   Develop techniques for assessing hepatocyte function prior to transplantation.
   Develop new cell sources for transplantation.
2. Develop a better understanding of the human liver diseases as they pertain to cell transplantation and develop improved animal models of human liver diseases.
3. Research into human liver biology and physiology with humanized mouse models.

1. Improve Cell sources for Transplantation.

The major impediment to expanding the use of hepatocyte transplantation (Htx) to larger numbers of patients is the lack of useful cells. To improve the cell sources for transplantation we focus trying to assess and improve the existing source, adult human hepatocytes, and also to develop potential new sources of cells for transplant such as fetal and neonatal liver, and stem cell sources from human amnion epithelium (hAE) or human ES or induced-pluripotent stem cells (iPS).

a) Optimize Tissue Digestion. The first studies we are, and will continue doing, to improve the existing cell source (human liver) is to work with a small biotechnology company to develop and optimize a new mixture of highly purified enzymes for liver tissue digestion that are optimized for cell isolation while being produced under GMP conditions so that it can be used for clinical Htx, With constant feedback from our laboratory on the results of different mixtures, we have helped formulate a mixture that digests human liver well and provides cells with high viability and plating efficiency. These studies are critical because there is only 1 source of GMP grade enzymes for tissue digestion. It is absurdly expensive and was formulated for islets and does not work well on human liver. When complete, we will have identified the proper mixture of highly purified, specific digestive enzymes that are optimized for human liver cell isolation. The entire field of Htx will benefit from these studies (1-2 years).

b) Develop Methods to Assess Liver Function Prior to Transplant. In my experience, there is little time between the isolation of cells for transplant and their actual use in the procedure. Thus, techniques are badly needed to assess liver function prior to Htx to insure that they will be useful for Htx. Our laboratory has considerable experience with the use of human hepatocytes for basic science, mainly CYP450-mediated drug metabolism and induction studies (see CV). Based on this experience we are developing methods to assess hepatocyte function with tests that can be completed within 2.5 hrs of isolation. These tests also must assess a broad range of liver functions. In addition we propose to miniaturize these assays when possible with methods that can be completed with fewer than 100,000 cells and formatted to 96 well-plates for ease in reading results. We are examining HPLC-based, fluorimetric and also colorimetric assays for applicability, sensitivity and reproducibility. We recently have begun a series of experiments with luminescent assays which show great promise. These assays will be examined head-to-head on a series of human livers to determine which ones seem to provide the most reliable information, based on correlations with cell viability and plating cell efficiency. Assays being investigated include measurements of CYP450 mediated metabolism (4 families), so-called phase II or conjugation reactions, ammonia metabolism and apoptosis assays. We will investigate ATP assays and some more directed towards specific metabolic liver diseases such as UGT-1A1 assays that would predict efficacy of the cells for transplants into Crigler-Najjar patients. Although not an immediate goal,

we will also work to optimize cryopreservation techniques with human hepatocytes. These cells generally do not freeze well and a variety of approaches with cryo-solutions and freeze rates will be the initial approach. The aim of this research is to establish "Release Criteria" for the cells that can be written into Htx protocols and provided to the regulatory authorities. These release criteria will form the basis or acceptance or rejection of the cells for eventual human transplants. These assays and criteria will be shared with other transplant groups throughout the world to help all of us interpret the quality control data generated by each center. As a final step of this quality control section of research we will develop an engraftment assay. All previous short-term tests are conducted to predict which cells will perform best following transplantation into patients. Our eventual goal will be to establish the release criteria as described above and to develop an assay that measures sustained engraftment of the human cells into immunodeficient animal. Initial studies will examine 30 day (and perhaps longer) survival, post transplant into SCID mice. Different sites such as under the kidney capsule, single or multiple liver lobes, spleen and perhaps subcutaneous fat pad injections will be examined for ease, reproducibility and sensitivity. This is considered to be a critical future goal of my research, to find an engraftment assay that can be implemented with each series of cells that are actually transplanted into patients. As data is accumulated, we will eventually determine which release criteria and engraftment assays provide the best prediction of eventual function in patients.

c) Alternative Sources of Cells for Transplantation.

One of the advantages of cell rather then organ transplants is the ability to use different sources of cells for the procedure and to incorporate new developments such as stem cell sources as they become available. To overcome the shortage of cells for Htx we propose to examine a series of different cell sources, fetal and neonatal hepatocytes, stem cells from human amnion, and other pluripotent cells such as human ES and iPS generated stem cells. As most of the transplants we propose to conduct involve patients with metabolic liver disease it is not clear that donor hepatocytes would have a growth advantage over the native cells. (This important assumption will be directly examined see Aim 4 below) Thus, following transplantation there may be little stimulus to proliferate. In preliminary studies, following transplants into SCID animals fetal hepatocytes were found to proliferate for several months following engraftment that resulted in 20-30 times higher levels of repopulation of mouse liver than was observed when equal numbers of adult hepatocytes were transplanted. Based on RNA studies, we could determine that the fetal cells also differentiated following Htx. These results suggest that we could transplant 20-30 times fewer cells and obtain the same levels of repopulation, or get 20-30 times higher levels of repopulation of patients than if equal numbers of adult cells were transplanted. Since only small numbers of cells can be isolated from fetal liver, we may have to try to expand the cells in 2D or 3D cultures or bioreactors to provide more cells for transplants. A similar but largely unused liver tissue resource is neonatal livers. There are many deaths in the neonatal period from a variety of causes that not used for whole organ transplant because of the size. Most would likely be quite useful for cell transplantation. We will also have to work with the organ procurement agencies, neonatologists and NICU staff, neurologists and pediatric hepatologists and PICU staff to help identify potential tissue donors and access this largely unused resource. We have experience with the isolation, cryopreservation and actual transplant of these early pediatric livers and have found them to be quite useful for every application studied. These fetal and neonatal livers should be particularly useful for transplants of neonates with life threatening metabolic liver disease or acute liver failure. Each cell type will be examined with the release criteria and engraftment assays described above to establish function and potential efficacy following transplantation. An alternative source of cells for transplantation is pluripotent cells isolated from human amnion epithelium. We were the first to discover and report the stem cell characteristics of these cells (Miki et al). They express surface markers and genes commonly observed on human ES cells (SSEA3,and 4, TRA-1-60, or 181, Nanog, Oct-4, Sox-2, Rex 1), but are not immortal or tumorigenic when transplanted. These differentiate to all three germ layers (pluripotent) and when cultured under

specific conditions, they express virtually all genes expressed in normal human liver. In preliminary studies, following transplantation into SCID mice they were found to express mature liver levels of 31 of 32 genes examined, including most genes deficient in metabolic disease patients (only UGT1A1 was lower). Thus hAE may be quite useful as substitutes for human hepatocytes in Htx.. We recently reported that hepatocyte transplants extended survival and largely corrected the imbalances observed in plasma and brain amino acids and neurotransmitters in a mouse model of MSUD (Skvorak et al., 2009a,b). In exciting preliminary data, we have found that hAE transplants work as well as authentic hepatocytes at extending survival. Amino acid and neurotransmitter levels are being examined now. We will continue this exciting area of stem cell research and will focus on, in vivo, differentiation of the cells and on the attempted correction of mouse models of metabolic liver disease with hAE (MSUD, PKU). While embryonic stem cells are also a potential resource that we have examined (Besma et al., 2009), we believe that iPS will play a have more important future role in regenerative medicine. We recently received substantial NIH funding for this line of research and within 1 month made 3, iPS lines from human hepatocyte cultures. We also have additional lines previously made from human fibroblasts, and are beginning characterization of the lines for complete reprogramming and for their ability to differentiate to hepatocytes. We will begin with the differentiation techniques we established in Besma et al., and will modify our differentiation protocol as needed and as directed by the results of the research. The ultimate goal of establishing iPS cells is for autologous transplantation of cells in patients with metabolic or chronic degenerative liver disease. Future plans for patients with metabolic liver disease would to make stem cells from biopsies of their liver or fibroblasts, correct the genetic alteration present in the genes causing their disease, and then differentiate the stem cells back to hepatocytes for future autotransplant. Although it seems fictional, it could actually be accomplished with technology that already exists. Approached for genetic corrections would likely include homologous recombination techniques, and possibly gene therapy involving viral or plasmid transfection. We are not skilled in these repair technologies and will need to collaborate with more skilled researchers when we have the mutations in our iPS cells characterized from patients with metabolic liver disease.

2. Develop a better understanding of the human liver diseases as they pertain to cell transplantation and develop improved animal models of human liver diseases.

The target population for most of our transplants will be patients with metabolic liver disease, thus we will investigate these diseases in a variety of ways. Unless the metabolic liver disease results in acute liver failure, fibrosis or cirrhosis, such as with tyrosinemia type 1, or A1AT deficiency, is it generally believed that there is no liver pathology associated with the defect. Htx will work best when there is ongoing cell death of native hepatocytes and sustained growth stimulus to donor cells, such that over time, the native liver becomes replaced with normal (donor) hepatocytes. It is believed, based on the absence of liver pathology that there normal cell turnover rates with most metabolic liver diseases. However with high amino acid levels observed with MSUD, or organic acidemias, or even with PKU, it seemed to us that there might still be significant cell turnover of the liver of these individuals. Based on these assumptions we have begun to study the available mouse models for metabolic liver disease and in preliminary results, have found that there are frequently 5-30-fold increases in the rates of apoptosis (based on tunnel positive cells) and a similar increase in the rate of cell replication (based on Ki67 positive cells). These results suggest that there is significant turnover of hepatocytes in these metabolic liver diseases even when they do not progress to fibrosis, cirrhosis or liver failure. This also suggests that normal donor hepatocytes that do not express the mutant gene might demonstrate a growth advantage if they were transplanted into these animals. We propose to examine liver tissue from representatives of every metabolic liver disease group for tunnel and Ki-67 analysis. We will also quantify the rates of replication of native and donor hepatocytes (tagged), post transplant, to directly measure the relative rates of replication of each cell type. In parallel studies we will establish ethical permission and IRB approval

to examine blocks of tissue from patients with these liver diseases to conduct the similar analysis. We will determine of the Tunnel and Ki-67 assays will be useful to predict a growth advantage to donor cells. If so, this simple procedure could be implemented on a case by case basis, where a biopsy from a patient considered for Htx therapy might be examined to determine the relative growth advantage we might expect post transplant. This could also be a method to stage patients and choose the candidates most likely to respond to Htx therapy.

2-b) Develop Improved Animal Models of Human Liver Diseases

The liver performs over 3,000 functions critical to maintaining the organism, ranging from production and secretion of proteins such as albumin, clotting factors and antiproteases, to metabolism and excretion of exogenous compounds such as drugs or toxins as well as endogenous compounds like hormones, bilirubin and bile acids and cholesterol. Liver-based metabolic disease can result from mutations in genes in these critical pathways. Transgenic or knock-out mouse models have been created for many of these diseases, but they do not always faithfully reproduce the human disease. For example mutations in the bile salt export pump (BSEP) results in severe cholestasis and fibrosis in human patients requiring whole organ transplants, yet the knockout mouse is nearly without a phenotype. While many patients with alpha-1-antitrypsin (A1AT) deficiency develop liver fibrosis/cirrhosis requiring liver transplantation, the transgenic mouse model carrying mutant human genes shows an extremely mild phenotype. The mouse model for a deficiency of ornithine transcarbamylase (OTC) activity, the rate limiting step in ammonia metabolism, is useful, however the animals tolerate a diet containing normal amounts of protein, while severely affected human patients require severe protein restriction to prevent lethal hyperammonemia. Mice (and rats) are particularly poor models for studying liver fibrosis and cirrhosis, common features of many human liver diseases. "Humanized mice" may offer a platform to both the study and treatment of metabolic liver disease and hepatic fibrosis and cirrhosis. Thus in a recent grant application we proposed, the hypothesis, that the best models for human metabolic liver disease are those created from the affected human hepatocytes. Thus, we proposed to" humanize" the liver of FRG mice by transplantation of affected human hepatocytes to create authentic models of human metabolic liver disease. These mice are immunodeficient and also deficient in the tyrosine catabolic enzyme, fumarylacetoacetate hydrolase (Fah -/-) and develop irreversible liver failure if left untreated. However, if Fah-proficient cells are transplanted, they readily and rapidly repopulate the native liver with donor cells, even if the donor cells are of human origin (a). To create these models, the liver of FRG mice will be "humanized" with hepatocytes derived from patients with metabolic liver disease. In addition, iPSC technology will be utilized to reprogram the liver cells from metabolic disease patients and following hepatic differentiation, additional mice will be humanized with iPS-derived hepatocytes. These humanized mouse models can then be compared to the authentic diseased liver with respect to changes in clinical chemistry (of the patient or animal), the histopathology of the liver and gene and protein expression profiling of liver tissue. In this manner, we will be able to determine if the humanized models developed with these procedures faithfully reproduce the phenotype observed in the patient. In addition to the direct effects on metabolic liver disease, success with these models will facilitate the use of humanized mouse models to investigate other liver based diseases such as Wilson's and Alpha-1-antitrypsin deficiency and may even lead to better-humanized models for primary liver cancer, acute liver failure and viral, alcoholic and autoimmune hepatitis and even the hepatic stage of malaria, especially if a human immune system were reconstituted in addition to the liver. Reconstitution of the liver with normal hepatocytes could provide useful animal models for research into the pathology and treatment of fibrosis and cirrhosis. These humanized mouse models of metabolic liver disease can form a platform technology to study gene and cellular therapy in models particularly relevant to patients. As described above, using iPS technology we propose to correct the genetic defects in metabolic disease patients and to examine the correction and function of the cells in this mouse model. This project was recently funded

by NIH.

3. Research into human liver biology and physiology with humanized mouse models

Using the FRG mouse as described above (and Azuma, et al.,), we believe that we can also make relevant humanized mouse models for the study of human biology and physiology. As this model is new, we need to characterize it mode completely. First we propose to transplant a series of animals with the same donor human hepatocytes and harvest liver tissue at specific times and examine the gene expression profile of the resulting mice by gene array and quantitative RT-PCR to determine if the phenotype of animals derived from the same donor cells are similar to each other, and also to the donor liver. Additional studies will examine serial transplants. Since the FRG mouse is a knock-out there can never be competition between the cells in the mouse liver and donor hepatocytes. This unique feature of our model (not contained in the previously established uPA-SCID model) allows serial transplants, that is, harvest of hepatocytes from one humanized mouse to generate more mice by transplantation of cells into additional recipients. This allows the maintenance of useful human cells beyond the lifetime of the recipient mice and could afford an almost limitless number of duplicate animals for study. However, like the primary recipients (above), we need to characterize the 2nd, 3rd and 4th generation mice and examine the gene expression profile of the resulting mice by gene array and quantitative RT-PCR to determine if the phenotype of the primary cells are maintained through serial generations of animals. We will characterize the gene profile and also analyze the metabolic capacity of the human hepatocytes isolated from representative animals. We will focus on CYP450 gene expression and induction, phase II conjugation pathways and liver transporter expression and function. We propose that we could examine human hepatocellular carcinoma formation, following exposure to agents such as Aflatoxin B1, a proven human carcinogen to which human cells are extremely sensitive whereas, mouse liver is considerably more resistant. Thus, we could establish the first mouse model to investigate human liver carcinogenesis. In addition to metabolic studies, these mice offer some unique insights in hepatic biology and physiology. In initial studies we have determined that as the liver becomes humanized, that mouse bile acids are replaced by human bile acids in accordance with the level of repopulation with human cells. Thus, these animals have humanized enterohepatic recirculation of bile acids and these mice offer unique access to the investigation of hepatic uptake and excretion of bile acid and other agents such as hormones, or drugs in human cells, *in vivo*. Additionally, we have observed that as the level of human hepatocytes increase in the mouse liver the cholesterol levels in the mice raise to levels normally observed in humans, thus they increase from range of 10-20 in mice to the 150-300 range as observed in humans, thus these animals might be useful models of hepatic cholesterol biosynthesis and elimination, and perhaps even the vascular effects of excess cholesterol. Once characterized in greater detail as described above, I believe these humanized mouse models will become tremendously valuable for the investigation of CYP450 mediated drug metabolism and elimination, hepatic toxicity of administered drug or chemical agents, the investigation of human viral pathogens such as Hepatitis B and C and a variety of normal processes in the liver such as insulin signaling and resistance, clotting processes, hepatic fibrosis and cirrhosis and a variety of other normal and disease processes not even considered here.

The brief descriptions above only serve as a general outline of proposed future research. While some are more at a basic science stage, such as the humanized mouse studies, most of the remaining studies are directed towards basic and clinical research to support the hepatocyte transplant program.